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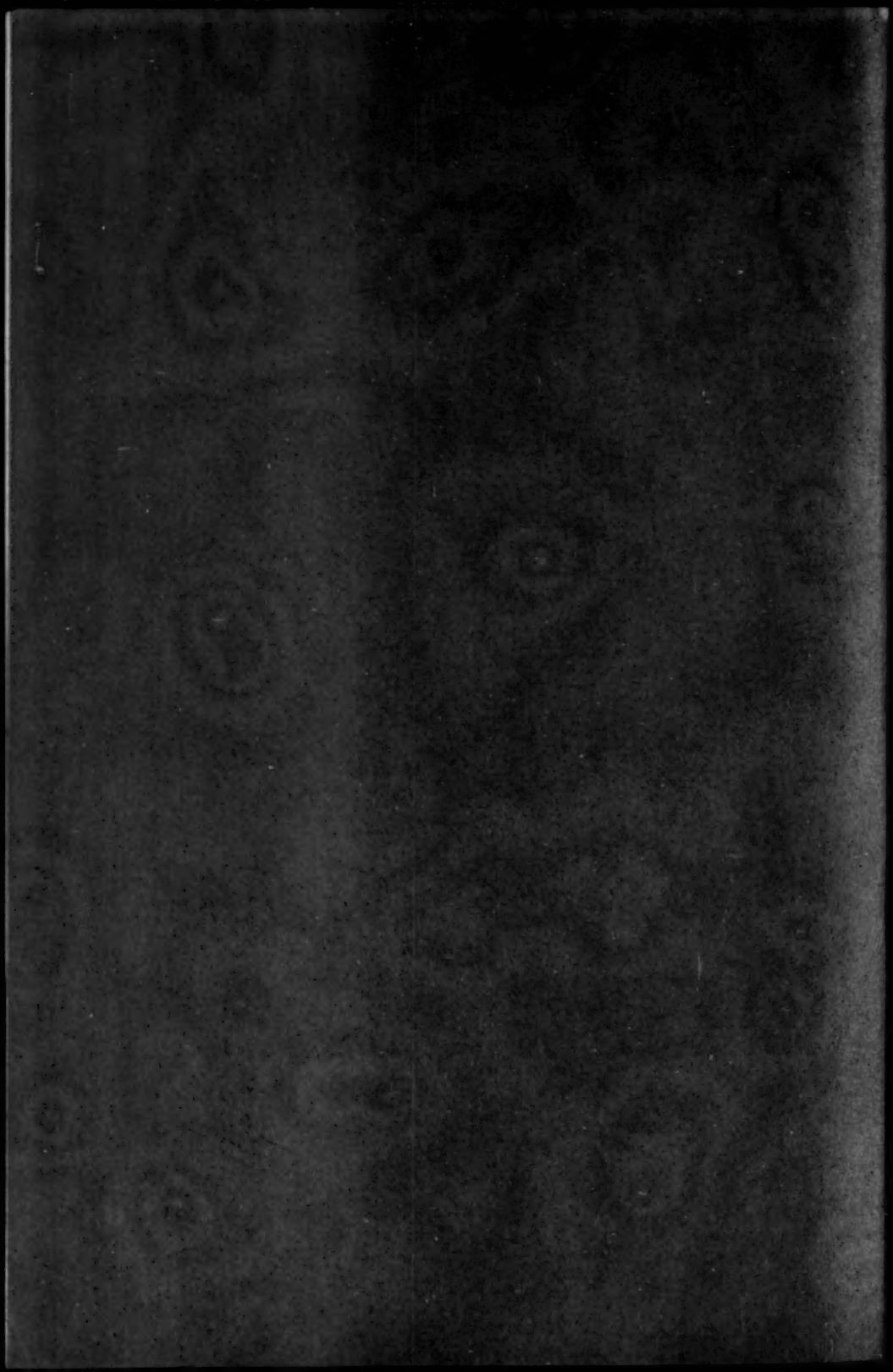

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JANUARY, 1943

THE PRINCIPLES OF TREATMENT OF CLOSED HEAD INJURY*

D. DENNY-BROWN

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HEAD injury has from time immemorial been considered a province of surgery, indeed any case may require skilled operative intervention. It may therefore seem odd that a neurophysician like myself should present views on this subject. In defense however I would invoke the authority of no less than Richard Bright, he that first described chronic nephritis, who says "Yet I think it right not entirely to pass over these accidents because they frequently lay the foundation for disease which the physician is called on to alleviate." In that same volume in 1831, Bright[1] proceeds to give the first description of traumatic petechial haemorrhages. The neurologist who has habitually assisted in the problems of severe head injuries may also be expected to have his own views on their treatment.

Closed head injury, for the purpose of this discussion is taken to mean a head injury brought about without break in the scalp. The importance of making this distinction is to exclude the question of treatment of scalp wounds, and penetrating wounds of the skull, which

* Read October 12, 1942 at the fifteenth Graduate Fortnight of The New York Academy of Medicine.

raise an independent series of surgical problems. Since scalp wounds are usually caused by the impact of some sharp edged object, closed head injuries are sometimes spoken of as "blunt head injuries," which we shall assume are the same thing.

At the beginning I would make it clear that head injury, even the subdivision closed head injury, is not a single pathological or clinical entity. Dr. Leary, in his masterly Ludwig Kast Lecture has shown us the variety of traumatic pathological conditions which may reside within the intact skull. It is clear for instance that cerebral contusion, subdural haemorrhage, and extradural haemorrhage can either singly or in various combinations arise without that immediate loss of consciousness which we call concussion. There is good reason to know that alternatively concussion can arise without any haemorrhagic lesion, as was maintained long since by Jonathan Hutchinson[2] and von Bergmann,[3] and demonstrated on an experimental basis by Polis,[4] Miller,[5] and ourselves.[6] Symonds[7] and Denny-Brown[8] have also reported instances of medullary lesions without other complications, and Denny-Brown and Russell[6] have reported instances of skull fracture and cranial nerve lesions from crushing injury without other complication, even concussion. We are not certain of the end point of what we term concussion, of which the clinical signs are largely negative—loss of consciousness and loss of reflexes. As John Hunter[9] has said "when there is depression of bone or extravasation the symptoms of concussion are lost, though it may be at bottom of all." I quote this opinion of over a century ago to show that what we consider is no new problem, that it can be as tough now as it was then.

It is not the place here to consider the various clinical states which may be associated with each of these various complications of head injury. Nor do I think it worth while to list each complication of head injury and its appropriate treatment, for the treatment of each singly is well founded and straight-forward. The difficulties encountered in practice are mainly traceable to the admixture of one entity with another, the confusion of signs and symptoms which betokens the mixture in pathology in all severe head injury. Allow me then to consider these mixed clinical states and discuss their treatment in relation to possible pathologies, for this is the way we meet the problem at the bedside.

The most obvious phenomenon in most head injury is *unconsciousness*. It is a condition which is defined in negatives, the absence of con-

sciousness, the absence of reaction, the absence of memory. In order to make myself clear I shall adopt the classification recommended by the British Committee on Brain Injury[10] and speak of *coma*, as a condition of lack of all reactions except the elementary corneal, tendon and flexion reflexes, of *semicoma*, as being coma with the addition of ability to make simple reply to painful or forceful stimulus, and of *confusion* to cover the lighter degrees of loss of awareness up to and including states where the only defect is one of loss of judgment or lack of appropriate behavior.

The treatment of *coma* begins immediately following head injury. It is associated with loss of all reflexes for an interval, and importantly for first-aiders, with loss of swallowing, so that the first attempts to administer fluid by mouth should be with the head turned on one side so that fluid may run out of the mouth if deglutition does not occur.

In immediate traumatic coma, or concussion of severe degree there is a great fall of blood pressure, with peripheral constriction of vessels, lasting some 10 to 30 minutes. This preliminary shock then passes off rapidly and considerable peripheral congestion with rapid pulse and rapid shallow respirations supervenes. This state need give rise to no alarm, and in simple concussion is the prelude to restlessness and semicoma, finally confusion, leading to recovery. There is little time for haemoconcentration to occur so that in the absence of wounds transfusion is not usually necessary, though moderate warmth and flat posture should be maintained.

In all very severe injuries stertorous and slow respiration, spontaneous deviations of the eyes, sometimes twitching of the limbs or face soon occur as the primary shock passes off and indicate that some immediate and grave contusion of the base of the brain or brain stem, usually with massive haemorrhage at the base is occurring. Coma is profound from the beginning and the pulse remains feeble. Such cases seldom survive more than a few hours, and no treatment is of any avail. The temperature may show a precipitate final rise. Lumbar puncture will withdraw darkly blood-stained fluid without relief of symptoms, dehydration makes no difference, nor are the contused vital centres amenable to direct surgical attack. If a head injury is severe enough it will kill, in spite of medical heroics. Such cases account for the high incidence of death in the first two days, as indicated by Jefferson.[11]

Short of such calamity the profound coma of concussion progress-

ively lightens. The corneal reflexes become more brisk, within two or three hours some reaction to a painful stimulus will occur, and a steady regular respiration is interrupted by such a stimulus. The limbs begin to show postures and occasional movements, the face to wince, and for the first time hemiplegia if present can be observed by the lack of this posture or movement on one side, and the appearance of appropriate plantar response. From this time, which may be from one-half to six hours after injury, the study of these signs will give valuable leads to pathology and then to treatment. In addition we may investigate the spinal fluid. It is likely to be blood-tinged in nearly all injuries with coma lasting more than one hour. The pressure ranges between 200 and 300 mm. in most of such cases. Let us consider three main possibilities:

1. Increase in comas, or in signs.
2. Increase in lumbar puncture pressure.
3. Progressive lessening of all signs and symptoms.

1. Increase in Comas, or in Signs

The classical description of the clinical condition of *epidural, or extradural, haematoma* includes what is called the "latent interval," a space of mental clarity following head injury, followed by the appearance, or renewal, of stupor. The duration of this latent interval obviously depends on the time taken by the haematoma to raise intracranial pressure to a critical value. If severe concussion has occurred the coma of concussion may last over and merge with the coma of cerebral compression. This however is unusual, for extradural haematoma is caused by localized injury and such severe concussion by generalized injury. In any case the reversal of improvement should be apparent if close watch is kept on physical signs. A dilation of the ipsilateral pupil, a slowing of pulse rate or a rise in blood pressure may be late events, but for that very reason are not so reliable. The change in lumbar puncture pressure occurs in too brief an interval to be of value as a diagnostic. A transverse fracture of the temporal squama may serve to make the wary keep a closer watch on the nervous physical signs. The treatment is purely operative.

More difficult to assess is the more gradual failure in improvement in coma, or gradual late deepening in 24 to 48 hours or even longer, which betokens the formation of an *early subdural clot, or a collection of watery fluid* ("hydroma" of Naffziger.[12]) The presence of this condition

does not always give rise to increasing hemiplegia or delayed appearance of a dilated pupil, both of which indicate necessity for intervention. More commonly it is associated with the occurrence of a steadily maintained state of semicoma persisting over 24 to 48 hours or even several days. In other circumstances this period is associated with great restlessness, and the stillness and apathy of these patients is a striking feature. There has usually been facial or limb weakness on one side since the time the first movement has been observed. This is not due so much to the haematoma or hydroma as to the contusion and laceration of meninges which gave rise to it. The problem now becomes which is the cause of the lack of recovery, the contusion or the fluid collection? I am sure, both from having been brought up in close association with a conservative surgical school, and from having observed old dural stains and membranes in the autopsy room in patients no longer having any complaint referable to their old head injury, that these acute subdural haematomas and hydromas are by no means necessarily progressive and dangerous as are chronic subdural haematomas. They are seldom seen in autopsy of acute injuries, nor is the severe compression of the brain they might be supposed to cause if they are the cause of death.

Surgical opinion on the subject differs greatly since the classical monograph of Brion[13] in 1896. Munro[14] is a staunch advocate of early operative exploration in any prolonged unconsciousness. Browder and his associates[15] take essentially the same view, but use ventriculography in doubtful cases. Published figures show a high mortality after such operative relief in the first 24 hours (83 per cent, Laudig, Browder et al[16]) or even the first three days (e.g. 9 out of 10, Voris[17]). It seems doubtful therefore if the surgical relief of this condition had any effect on the natural course of the severe head injury in this early period. Voris[17] (1941) speaks even of filling the cavity previously occupied by the haematoma with water to induce swelling of the brain!

In relation to a failure of progressive recovery from coma therefore my attitude is conservative, and I would maintain nourishment while watching for change. Should signs of hemiplegia become more marked, or simple coma be steadily deepening, I should recommend exploration. But seldom have I seen dramatic recovery from steadily maintained coma by relief of an early subdural collection of fluid, and suspect an underlying contusion or lacerations to cause persisting symptoms. It is difficult to be convinced that operative relief of an acute subdural lesion

was necessary to save life, and then only when there was rapidly progressive late hemiplegia with very rapid postoperative improvement. It is of interest to find that this view was held by Bergmann and Wiesmann[18] in 1904 and earlier. These authors also note the tendency of these acute lesions to disappear and leave only a dural stain.

I am not convinced that dehydration affects such acute fluid collections though that is a possible rationale which may be advanced for dehydration. Little is understood of the absorption of fluid from the subdural space, but it may be pointed out that these acute subdural collections have little relation to any vascular bed and usually spring from some small tear in the arachnoid.

Also coming into the group of cases under discussion is a type in which some focal signs (usually facial weakness with or without dysphasia) are present immediately following the injury, may progress for an hour or two then remain constant for several days, with slight additional increase between the 5th and 10th days, without further impairment of consciousness. This late increase in signs may be of the order of transition from a slight dysphasia to a complete aphasia. There is usually an increase in blood in the spinal fluid after the first day, but no severe subarachnoid haemorrhage at any time. The inability to exclude the possibility of subdural haematoma usually results in exploration. The surgeon finds no haematoma, but instead a purplish discolored brain in the region of the Sylvian fissure. If the pia-arachnoid is sectioned clots will extrude, and the sucker will leave a great cavity far undercutting portions of frontal, parietal and temporal lobes. The haemorrhage in such cases I have seen explored has always appeared to me to be in the Sylvian fissure, from an oozing subpial and subarachnoid contusion in the region of the middle cerebral vessels. The natural resolution of such a condition appears often to result in better salvage of the neighboring tissue than does operation, and we have not been impressed by the immediate effects of operation.

An important cause of late increase in, or appearance of, coma is *fat embolism.* This complication is apt to occur on the second or later days, and in relation to pulmonary signs, swinging fever, cutaneous petechiae and fat in the urine. There may or may not appear fresh neurological signs, increase in CSF pressure, convulsions. A stormy and usually fatal illness results, but recovery with or without cerebral residua can undoubtedly occasionally occur. Hunt[19] reports such a case

without residua. Exploration reveals only increased subarachnoid fluid. No treatment affects the course of the illness. Various emulsants have been tried, some resulting in fresh symptoms as if more fat had been released into the circulation.

A possible but rare cause of persistent stupor or confusion is *pneumocele*, arising from suction of air through a fissure into the frontal sinus in a restless patient. This draws attention to the need for surgical repair of comminuted fracture of the posterior wall of the sinus. *Rhinorrhoea* from the same cause is a most significant symptom. If it occurs but once in the early stage, and there is but a simple fissure in the bone, I am not convinced that surgical repair is better than the normal dural healing process. But if rhinorrhoea or pneumocele occurs after the first week or if there is likelihood of prolapse of brain into the frontal sinus, surgical repair of the dural opening becomes an urgent necessity in order to prevent subsequent meningitis. It is most important to realize that this can occur in so-called closed head injury.

Last in this group I would mention a most disturbing but fortunately rare event—the occurrence of a *delayed traumatic hemiplegia.* I have seen two such cases in young men in each of which an original injury to the neck had been overlooked. In one of these a subsequent arteriogram by Cairns showed an occlusion of the internal carotid artery on the side of the lesion. It is obvious that the sequence of events was here damage to the intima of the carotid resulting in progressive clotting and eventual occlusion of the middle cerebral. This explanation could equally well apply to the other case, but with embolic hemiplegia, for the internal carotid was found to be patent, but distorted. In both cases such explanation is preferable to any supposed delayed direct damage to cerebral vessels, but in neither case can effective treatment be suggested. It might be noted in passing that a recent case of delayed hemiplegia reported by de Veer and Browder[20] also suffered an injury to the neck, though the event was attributed to middle cerebral thrombosis. Such delayed hemiplegia should not be confused with the very common delayed facial paralysis of peripheral type which is related to the liquifaction of clot in the middle ear and has an altogether benign course.

2. Increase in Lumbar Puncture of Intracranial Pressure

The lumbar puncture pressure is raised in many cases of severe head injury. The degree of rise is moderate, reaching less than 350 mm. in

almost all. A rising lumbar puncture pressure, plus an increased depth of coma is a combination that cannot be ignored, and requires surgical exploration. On the other hand a moderate increase of CSF pressure with lightening or even stationary coma is of benign significance. The cause of raised CSF pressure is then contusion. Experimentally the course of events in the development of contusion is slow. In animal experiment the disturbance we call concussion may be over by the time the contusion has appeared (Denny-Brown and Russell,[6] 1941). The immediate increase in pressure is small unless the basilar portions of a hemisphere are injured. Death rarely occurs from simple hemisphere contusion. Oedema surrounds the contused area. This takes several hours to develop, and its development in relation to medullary contusion is the presumed cause of death in the first 24 hours in severe cases without progressive haemorrhage. This reasoning has led to the employment of extensive dehydration by Fay and others. Unfortunately the results are exceedingly difficult to assess.

If we enquire into the reason for this difficulty we find immediately that there are several causes for confusion, and they are chiefly concerned with the definition of oedema, and what we might expect dehydration to accomplish. Thus

a. *Oedema is not to be measured simply by increase in intracranial pressure.* Thus for instance, the highest and most persistent increases in intracranial pressure are found in cases of occipito-parietal fracture with tearing, and later thrombotic obstruction of the sagittal sinus. I have seen such a case with papilloedema and a very high C.S.F. pressure lasting to the fourth week. There were no other signs and the patient sat cheerfully in bed, complaining only of not being allowed to walk around the ward. The degree of papilloedema was controlled by lumbar puncture until the hydrocephalus subsided naturally in the fifth week, probably from recanalization of the sagittal sinus. It was manifest that dehydration was unnecessary in such a case, that the brain was compressed by external hydrocephalus.

As Browder and Meyers[15] have indicated the rise of spinal fluid pressure in severe head injury seldom approaches the limits of diastolic blood pressure, at which it would begin to constitute a danger. The careful studies of Browder and Meyers have documented clearly what is evident to the careful clinical observer, that the classical signs of dangerous intracranial pressure, slowed pulse and respiration, rising systolic

pressure, are extremely rare, and do not usually herald the approaching end.

It has been shown elsewhere (Denny-Brown[8]) that the most remarkable slowing of the pulse in cases of head injury can occur when there is no question of critical intracranial pressure, and is related to medullary contusion.

b. It has already been mentioned that a contusion itself by reason of its contained extravasation of blood, increases pressure in moderate degree. This blood extravasation is not affected by dehydration, nor is the loss of nervous function in the area thereby recovered. The initial direct contusion symptoms are therefore not affected by dehydration, and take some 3 to 6 weeks to subside. We cannot expect to heal a bruise by dehydration. Yet it seems that immediate betterment or complete relief of symptoms is expected, or even reported, following dehydration. That can only occur through misconception of pathology.

c. If dehydration is to have obvious effect its logical place is in combating the progress from deep stupor to deep coma that occurs between the 6th and 48th hour after very severe head injury, and which all are agreed to call "medullary oedema." Occasionally it is a ventricular haemorrhage in disguise. But dehydration, if it has effect, will only restore the stage of deep stupor, or prevent the dangerous worsening.

d. Dehydration of degree sufficient to be worth while in this connection is not itself without dangers. In all severe head injury there is a period of immediate and profound fall in blood pressure lasting several hours. This appears to be a variety of "primary surgical shock." When there has been exposure to cold a period of secondary surgical shock occurs, as with other wounds, with corresponding haemoconcentration. This condition is in no way benefited by dehydration. There is no information as to the relative interaction of these two in head injury and further studies are badly needed. I can report however that in severe head injury with traumatic delirium I have seen manifest immediate general improvement and subsidence of restlessness, without change in physical signs, with cessation of dehydration.

e. It is necessary to emphasize that dehydration has no effect whatever on the steadily improving course of mild head injury—except to worry the patient and increase restlessness. Headache of post-lumbar puncture type, hypotonic postural headache, is often a troublesome sequel to unnecessary dehydration.

The place of dehydration therefore is the possible prevention of "acute medullary oedema" and in this it appears remarkably inefficient. In other types of cases there is no clear conception of what dehydration accomplishes. All statistics in this connection are confused by the inclusion of cases of less severity, which in any case run a milder course. Further accurate studies on shock are desirable.

This section of my discussion was concerned with increased intracranial pressure. To identify such increase with a hypothetical "oedema" only blinds us to its varied causes. There is no well founded state of traumatic oedema apart from that accompanying contusion. Let us rather persist in seeking features which will indicate the true pathology which I am sure differs from case to case, but of which the most significant ingredients are contusion, or damage to venous drainage.

3. Progressive Lessening of All Signs and Symptoms

It has been clear since the first writings about head injury by Paré[21] and others that certain milder kinds of head injury, even with loss of consciousness, undergo a steadily progressive improvement and eventual recovery, without evidence of any persistent damage. To such cases, without other clearer definition the term *concussion*, or *commotion*, of the brain was applied. Many have doubted the existence of such an entity, saying where is its pathology, how can such a profound disorder have no pathology. A disorder without histological basis is certainly a challenge, but it must not be forgotten that such well recognized conditions as tetanus, or epilepsy, also lack a histological basis in morbid anatomy. That is not to say that they do not exist. Recently I have attempted to give the condition concussion more concrete definition in terms of nervous function by experimental means (Denny-Brown and Russell,[6] Williams and Denny-Brown.[22]) It is maintained that it is a type of traumatic paralysis which undergoes spontaneous resolution, with perfectly clearly definable sequence of events in terms of the E.E.G. and of reflex function.

The question that has exercised all minds dealing with this problem is "How long can concussion last and still not be complicated by other more serious haemorrhagic lesion?" I would answer, first that concussion is one of a series of components of head injury, and may coexist with any of the others, some of which also cause unconsciousness, so that to my mind the question should be "How are we to know when concus-

sion overlaps with other complications, and for how long can concussion account for unconsciousness?" I put the question in this way because that is how it affects our management of head injury, and because until recently loss of consciousness was the only criterion of concussion.

With the development of electroencephalography and air encephalography it has become realized that there occur a group of cases of prolonged coma followed by delirium and confusion, the whole disorder gradually subsiding in days or weeks, without evidence of focal lesion at any time. Furthermore the generalization of very slow waves in both hemispheres in the E.E.G. in these patients, throughout the amnesic period provides positive evidence of a general pathology. A laceration of the brain shows a local disturbance. Thus there is fairly good evidence that such a condition of traumatic coma and confusion can be due to some generalized physical disorder of the cerebrum rather than to any haemorrhagic lesion. In the absence of increased intracranial pressure, or localizing signs, and in the presence of a generalized slow wave E.E.G. disturbance, coma can therefore be expected to make a slow resolution without operative interference. Dehydration is without effect in these cases. They are primarily a nursing problem, though the restlessness and delirium, particularly at night, requires sedation and the intelligent use of fluids and nourishment. Restraint is preferable to a very heavy sedation over a long period. It is important to exclude distension of the bladder as a cause of restlessness.

In all cases where there is embarrassment of respiration morphine is contraindicated, and chloral-bromide or paraldehyde used. When scalp wounds have occurred and loss of consciousness is no deeper than stupor, British surgeons commonly use small to moderate dosage of morphia to control restlessness. I have never seen disadvantage from such use of morphia, though I am aware of resistance to such use in this country. The effect of any sedation in making changes in the degree of coma must be allowed for.

In such cases, the possibility of subdural haematoma is one that continually exercises the doubts of the attending physician. One useful point is that restlessness and delirium are extremely uncommon in the presence of a dangerous haematoma.

It is of course possible for such a maintained concussive state to coexist with other complications such as haematoma, contusion or laceration of the brain. That these are not more commonly mixed is I think

due to the fact that such lesions as contusion laceration and extradural haematoma result usually from very localized violence, whereas concussion is due to the general shaking of the brain. Few injuries provide both factors in severe degree. But the smaller acute subdural haematoma may complicate concussion. If it does it is seldom of consequence, and no direct lightening of consciousness follows its drainage.

But mixtures of prolonged confused states due to concussion, with the condition called chronic subdural haematoma occur as frequently as with acute subdural collections. In some surgical writings on the subject (Kaump and Love,[23] Holt and Pearson[24]) it is sometimes assumed that the confused mental state is due to haematoma. In assessing treatment it is important to assess the ingredients of such pathological mixtures separately.

The main principle here is that generalized traumatic coma is a progressively recoverable condition, with slow improvement from day to day. It is useful to have simple means of recording the depth of coma. I would suggest a series of graded tests such as:

1. A reaction to a question such as, "What is your name?" spoken in an ordinary tone of voice.
2. An imperative question spoken loudly.
3. The reaction to a painful stimulus.
4. The presence of the corneal reflex.

In this way the change from less to greater reactivity can be more accurately observed.

So slow may the natural improvement be that only by comparing the receptivity and orientation of the patient day by day can the improvement be seen. On the other hand any regression, any loss of ability once regained should lead to suspicion of some progressive haemorrhagic lesion. This is the cardinal principle in treating these cases. Until some means of treatment can be shown to be statistically significant in hastening recovery, or unless there is good reason to suspect a dangerous complication, their treatment becomes that of the management of the comatose or confused patient. A wit has called this "intelligent neglect," but even so I would prefer it to pointless interference.

Apart from the dramatic surgical intervention in the dangerous complications of head injury, the next most important treatment is what might be called "prophylactic psychotherapy." Many forget that head injury is an acute emotional as well as an acute physical crisis. From the

moment that the patient becomes conscious, lability of the emotions, lack of confidence and insomnia betray the damage to the psyche. These can and should be met at the time by reassurance and discussion and by rationing of mental effort and excitement. Where post-traumatic amnesia has been prolonged intellectual impairment is to be expected in the convalescent stage and the patient's activities must be graduated within his reduced capacity. With simple psychotherapeutic watchfulness against the patient's secondary anxieties as to his head and his occupation in the early stages much of so-called "post-traumatic neurosis" could be avoided.

Finally, even in quite mild closed head injury, a very *labile vasomotor reaction* is extremely common in the first two or three weeks following injury. It is seen chiefly in the form of labile pulse and liability to syncope (Denny-Brown[8]) and is due to concussion or contusion of the medulla or upper cervical cord. It is the chief reason for the clinician's empiric insistence on complete rest in bed for this period. Each case must however be judged on its own merits, for head injury is a mixture of so many separate factors, and it is as unwise to keep a very mild case in bed for four weeks, as it is to allow a severe case with prolonged amnesia and confusion up after one week.

Conclusion

It is concluded that the time is ripe for a stocktaking of our present methods of recognition and treatment of the complicated condition we call "head injury." Against some of its chief immediate dangers we have little remedy. The opening days of this century witnessed a famous polemic between von Bergmann[3] who maintained that the theory of head injury centered around concussion, and Kocher[25] who emphasized increased intracranial pressure. Your own Drs. Browder and Meyers[15] and Munro[14] have assailed Kocher's clinical criteria of compression. I am doubting the vascular factors which were also a vital part of Kocher's theory. In fact I find myself in substantial agreement with most of the views expressed in the last American edition of Bergmann's famous textbook,[18] published in 1904. Let us take this as a challenge and set vigorously to work. It is maintained that a good starting point in clinical practice is more careful gradation and observation of the state we are apt to call "unconsciousness," analysis of which can be a valuable clinical sign.

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THE USE OF VITAMINS IN CLINICAL NEUROLOGY*

The Wesley M. Carpenter Lecture

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To obtain an equitable understanding of nutritional disease it would seem desirable to have worked in regions where such diseases are endemic. This premise holds generally, to be sure, for an understanding of tropical disease. It should not be intimated that malnutrition is a monopoly of any one section of this country, though it is probably not amiss to think that food habits might be. At the least there would appear to be staples of food which are basic in the diet in certain regions of the United States. Examples readily come to mind.

It is within the experience of all of us that allowed choice of food within a certain price range, the dietary does not differ much from day to day. Emotional factors are potent in the choice of food. Astonishing food habits develop of which the habitue is not particularly conscious. To many persons what is eaten is not as important as with whom it is eaten, a point which has more connotations than the obvious one. It is possible that the bonds of habit are as much responsible for the amount of unadulterated nutritional deficiency observed in the southern United States, as is poverty.

Whatever may be thought of this philosophy there will be little argument with the fact that diseases dependent on inadequate ingestion of nutrition are best seen in their elementary form in the southern United States. At the risk of seeming ostentation, it may be observed that one hasn't seen and doesn't understand many of the practical factors of adult human disease incident to malnutrition in this country, until he has served a spell in the South. Certain it is that many of the misunderstandings that surround the subject would be liquidated by such

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experience. One would then be unlikely to include under the heading of human nutritional disorder diseases which are not readily observed in the locales of their greatest incidence.

It has been noted widely that nutritional disease may occur in the face of a normal intake of food. Thus diarrhea, interference with absorption, failure to convert vitamins into absorbable substances, the inhibitory power of infection, congenital requirement for abnormally high intake of certain dietary factors, an increased demand for vitamins to detoxify poisonous compounds, and excessive sweating have been considered capable of producing nutritional deficiency even though the individual is eating normally. Nevertheless the fundamental and best understood nutritional deficiency diseases are those which follow rather directly on the inadequate intake of accessory food factors. Less conjecture surrounds their physiopathology and when neurological disorder develops in their wake, cause and effect appear to be obvious.

If one may dispense with all but a modicum of that emotion which usually wells at the mention of the vitamins, I would like to discuss briefly those clinical neurological states which are benefited by their exhibition. The discussion will be directed chiefly toward therapy. Slight mention will be made of those conditions which are not benefited by vitamins despite reports to the contrary. Finally interesting and provocative investigation on the subject will be touched on. It is obviously not possible to go deeply into any portion of the subject. In the interest of thoroughness the gamut of vitamins will be run, beginning with those of least use in clinical neurology.

Vitamin A

Despite the production of nervous lesions in animals by withholding vitamin A and the hope held forth, particularly in England,[1] that this substance might be of importance in degenerative nervous changes in man nothing has come of it up to now. Wolbach and Bessey[2] and Mellanby[3] demonstrated in young animals deprived of vitamin A that it was the disproportionate growth of the central nervous system in relation to the bone which surrounds it, which caused the nervous lesions.

Since vision is the particular province of the ophthalmologist, a discussion of night blindness and its relationship to deficiency of vitamin A is not in order. It is thought that vitamin A will improve the night blindness of nutritional deficiency.

Vitamin C and D

Deficiencies of these substances do not result directly in neurological disorder. The notion that vitamin C deficiency might be concerned in cerebral hemorrhage has not borne fruit.

It has been determined[4] that vitamin C deficiency is not the cause of hypertrophy of the gums in the dilantin therapy of epilepsy despite the early opinion to the contrary.

Vitamin E

Clinical work with vitamin E stemmed from the experiments of Einarson and Ringsted[5] who induced vitamin E deficiency in rats. The deficiency was associated with the development of lesions in the nervous system and muscle.

It is disheartening to have nothing good to say of vitamin E, which has been advocated in the therapy of amyotrophic lateral sclerosis and the muscle dystrophies. Our experience with amyotrophic lateral sclerosis has been just as sad since exhibiting this vitamin as before. Vitamin E has been used in both the natural and synthetic forms, with the disease in its incipiency and also advanced, and in the male and female patient. The gamut of dosage has been run, and it has been administered parenterally and by mouth. Surveying our work with vitamin E, it seems that we have answered every criticism of its adherents, and still found it to be wanting of any beneficial effect in the neurological diseases that beset man. This includes practically all forms of the muscular atrophies and dystrophies.

Vitamin B Complex

[B_1 (thiamine), riboflavin, niacin (nicotinic acid), B_6 (pyridoxine), paraminobenzoic acid, pantothenic acid, inositol, choline, adenylic acid]

The B complex of vitamins has an established reputation in the treatment of certain neurological disorders. The extent of its efficacy may be explored by systematically considering the neurological diseases of man associated with nutritional deficiency.

It is worth stressing that most, and probably all of the human nutritional deficiency diseases are the result of the deprivation of more than one vitamin. The concept of mixed deficiencies has been repeatedly

stressed in the clinical literature by Spies and his co-workers.[6] Wintrobe and his co-workers[7] have put the matter succinctly, "as to clinical observations, the assumption that in beriberi only thiamine deficiency occurs, implies on the part of the victim a knowledge of the distribution of vitamins in foods and an ability to select them which would be exceptional, to say the least."

The most striking response to vitamin B complex occurs in the neuritis of endemic pellagra and in the asthenia, multiple somatic complaints, and acute psychoses which sometimes accompany this mixed deficiency disease.

Neuritis: Neuritis is common in sufferers from pellagra.[8] It might be advisable to note several characteristics of endemic pellagrous polyneuritis to differentiate it clinically from other forms. The symptoms and signs of pellagrous polyneuritis are of the same kind, though of milder degree than those found in the other varieties. Despite the prolonged deficiency of nutrition which occurs in the great majority of endemic pellagrins, the polyneuritis though longstanding is rarely of great severity. In fact, I have never seen paralyzing polyneuritis in a pellagrin unless he had been ingesting alcohol or had some severe disease of other than nutritional origin.

Pellagrous polyneuritis responds readily to small doses of vitamin B_1 (5 mg. taken orally two or three times a day) if there is normal absorption. There is definite relief; leg pains remit promptly and these patients note strengthening of limbs that had been weak generally. The effect is prompt, usually within days the patient considers cured that part of his complex syndrome. Pellagrous polyneuritis is probably as close as we usually come to the neuritis of endemic beriberi in this country. It is said that neuritis occurs with some frequency rather early in beriberi, and that this type of neuritis if not too well established responds promptly to vitamin B.

It has been thought that the neuritis associated with prolonged ingestion of alcohol is closely akin to the deficiency neuritides. The clinical evidence for their intimate and complete relationship is not beyond reproach. In the first place, the neuritis associated with alcoholism is almost without exception, considerably more severe than the neuritis of endemic, non-alcoholic pellagra, if the latter disease may be used as an example of a typical nutritional deficiency. One cannot account for this severity on the basis that the nutritional deficiency, if this be the

etiologic factor, is more prolonged and profound in alcoholism. There is no deficiency of nutrition as prolonged as that seen in endemic pellagrins. Many of these people and their children subsist on grossly inadequate nutrition practically from the day of their birth.[9]

There is some experimental evidence which bears on the question.[10] Speidel[11] noted that an environment of dilute alcohol was deleterious to the nerves in the tail of the living tadpole studied by direct observation, despite the apparent well-being of the rest of the organism. More important he described the restoration of these nerves to normal when the tadpole was restored to its usual environment. Lowry, Sebrell, Daft, and Ashburn[12] observed that thiamine deficient rats on water, without exception developed a neurological disorder before paired, thiamine-deficient litter mates on alcohol or whiskey, in other words, alcohol or whiskey appeared to delay the onset of a neurological syndrome in rats. Their work indicates that the ingestion of alcohol in rats does not increase vitamin B_1 requirement. Whether or not they are producing neuritis or another complicated neurological disorder is a moot point. Some investigators[13] with neurological experience are inclined to believe that the disturbance which develops in rats deprived of thiamine is essentially vestibular in locale. Also, it should be mentioned that considerable species difference exists in the experimental production of polyneuritis. No one has yet reported having produced neuritis in man by the feeding of diets low in thiamine, though many have tried. There is considerable rumor afloat that it has been done but the experience has not been documented.

We are a bit afield from therapy, but this discussion leads directly there. Regardless of whether the neuritis associated with alcoholism is or is not a nutritional deficiency neuritis, its response to thiamine, or to mixed vitamins is indeed disappointing.[14] One may relieve the aching, boring, stabbing pain in these severely paralyzed neuritics, but beyond this relief not much need be expected. If alcoholic neuritis is dependent primarily on a deficiency of nutrition and if it isn't usually readily reversible, enquiry should be made into the wherefore of this irreversibility. Alcoholic neuritis cannot be closely compared from a therapeutic standpoint with a type of neuritis that is known to be due to prolonged nutritional deficiency (pellagra). Another profoundly paralytic form of neuritis, namely infectious polyneuritis, which also is not amenable to vitamin therapy, may be reversed rather completely in a few weeks,

even though its development in some cases apparently requires no less time than does the neuritis associated with alcoholism.

These features of neuritis would appear to indicate that another factor in addition to malnutrition is at work in the production of the polyneuritis associated with alcoholism. Nevertheless a nutritious diet should be given to these patients.[15]

It is probable that some common disorder of metabolism underlies all of polyneuritis[16] despite the apparent variance of precipitating agents, although the various clinical types respond differently to the exhibition of vitamin therapy.

Subacute Combined Degeneration of the Spinal Cord: The neuritis which accompanies subacute degeneration of the spinal cord which may or may not be associated with anemia, appears to respond to nothing besides liver extract administered parenterally.

We have had occasion to give brewer's yeast plus large intravenous doses of thiamine (50 mg. twice daily) to patients with posterior lateral sclerosis of the spinal cord associated with pernicious anemia. During the period occupied by this therapy the neurological signs progressed in severity, despite a reticulocyte response and an increase in the number of red blood cells.

Mental Symptoms of Pellagra:[17] In persons suffering from nutritional deficiency there may be a breakdown of the integrating forces of the personality with resultant mental symptoms. Their nature and severity depend on the structure of the personality previous to the disease as well as the intensity, duration, and abruptness of the deprivation of nutriments.

Mild Mental Symptoms: Among the comparatively milder nervous symptoms which may occur early in the course of pellagra, anxiety is an outstanding feature. Anxiety may range from apprehension and restlessness to anxiety attacks with severe respiratory symptoms and fear of impending death. The commonest complaint is nervousness; these patients are easily startled, excited, or irritated. They are sensitive to sounds which normal persons do not find particularly disturbing. They are easily frightened, and they avoid crowds. They feel sad; crying spells are a frequent manifestation. They have difficulty in maintaining attention and in concentrating. Dizziness and headache are common.

These mild mental symptoms of pellagra which in the past had been termed neurasthenia and considered a prodromal phase of pellagra, re-

spond either to thiamine or nicotinic acid. It must be remembered that pellagra basically is due to a deficiency of several essential substances and its complete relief requires more than a single vitamin. The reason for dual relationship of thiamine and niacin in the relief of the acute mental symptoms of pellagra is not explained on the basis of mixed nutritional deficiency. The reason for the favorable response to both of these substances is not known. The experience with a patient is illustrative of the rapid response obtained in undoubted nutritional deficiency disease.

Case 1. A 17 year old girl entered the Nutrition Clinic complaining of pain in the stomach severe enough to prevent sleep, and painful, cold, numb extremities, and bad nerves. The dorsa of the legs and feet had been red and had peeled several times during the preceding three years. Eight months before entry to the clinic she began to experience pain and nausea after eating. She had been nervous for seven months, frightened by noises and sleepless because of gastric distress and fear. She imagined that she heard bells and voices at night, and she had thought that she could see animals during the day. She had refused to be without a light at night, and she was constantly afraid to be alone. She suffered from palpitation and smothering spells, and feared death during these episodes. She was apprehensive of impending disaster for herself and her relatives. She noted impairment of memory. She could not tolerate noise, sudden noise caused starting. Odors produced nausea, and radio music was usually annoying. She had sensations of crawling and stinging in the skin. She was restless, couldn't stand or sit still, and she complained of fatiguability and weakness. She had dizzy spells. She sometimes staggered and at times felt as though she were walking backward. She suffered from headache. She had not attended school for 3 years because of the illness.

The symptoms were corroborated on physical examination, in addition she had tachycardia and signs of mild peripheral neuritis. She was extremely tense, restless, and apprehensive, and the face was drawn and worried, which made her look old.

One hour after the intravenous injection of 50 mg. of thiamine in 4 cc. of physiological saline solution, she was improved amazingly. She was alert and smiling and felt restored. She lost the apprehension and nervousness, and volunteered that if she could remain that way she would be well. The pulse rate decreased significantly. No more thiamine was administered and the syndrome was allowed to develop again, which it did with the exception of calf tenderness, within thirty-six hours. Four cc. of physiological saline solution administered by vein effected no change in her condition. One day later the intravenous injection of 50 mg. of thiamine produced improvement within twenty minutes and virtual "cure" in sixty minutes. She had changed from a state of quiet and morose fearfulness to one of cheerful and playful activity, willing to exchange repartee with the personnel of the clinic. In this instance she was told banteringly that if she did not begin the ingestion of red meats, and other foods rich in the B complex of vitamins, they'd be hauling her away in a box. She replied that she didn't care for that stuff, that "side meat" (pork) and corn pone more nearly suited her tastes. One soon learns the tremendous importance of food habits as well as poverty in the genesis and maintenance of pellagra.

This is the usual course of events in the experimental relief of the milder mental signs of pellagra. The rapidity of the restoration indicates the ready reversibility of the functional disorder underlying the symp-

toms. It is to be noted that neurosis and nutritional deficiency may coexist in the same person. A psychogenic disorder per se would not be expected to be cured by vitamin therapy.

The improvement is of course best maintained on a full, well-balanced diet, in the absence of which it may be fostered by small, oral doses of the vitamin B complex.

Severe Mental Symptoms: Among the most frequent psychotic manifestations of pellagra are confusion, disorientation, impairment of memory, hallucinations, and paranoid trends. The acute psychoses of pellagra usually resemble the conditions sometimes known as toxic psychosis, delirium, or organic reaction psychosis. The relief of the acute psychosis associated with pellagra can be readily accomplished with large doses of nicotinic acid, 100 mg. of nicotinic acid amide hourly during the day, allowing the patient to rest at night. The medication usually has to be given parenterally because of the inability of the patient to coöperate. The attempted therapy of acute and chronic mental symptoms, of other than nutritional origin, with vitamins, has been uniformly disappointing.

The chronic psychoses associated with pellagra are not benefited much by vitamin therapy.[17] The bedridden patient may become more alert and may be got out of bed. The association of pellagra and long-standing psychosis is not common.

Asthenia: In far advanced nutritional disease, particularly in pellagra there occurs sometimes an asthenic condition in which the patient becomes so severely emaciated that one wonders to see him live. These patients complain particularly of weakness, difficulty in walking, irritability, extreme nervousness, insomnia, and abdominal pain, and their gastric condition is such that the stomach no longer tolerates much besides milk. A single intravenous injection of 50 mg. of synthetic vitamin B_6 (pyridoxine) temporarily relieves the weakness and loss of confidence of this peculiar state[18] and may tide the patient over the institution of proper feeding. Possibly the reported efficacy of vitamin B_6 in some cases of Parkinsonism is due to this strengthening effect. A sedative effect has been noted in some persons; sleep being induced with large doses (100 mg.) of vitamin B_6.

Some patients with nutritional deficiency exhibit tremulousness, and slight resistance of the musculature to passive movement. Almost without exception they complain of being weak generally. Should nutri-

tional deficiency be grafted on a case of Parkinson's disease one would not be particularly surprised at temporary improvement with vitamin B_6. Certainly the two diseases may occur coincidently. However, the usual case of Parkinson's disease is not affected by vitamin therapy.

"Nicotinic Acid Deficiency Encephalopathy": Jolliffe, Bowman, Rosenblum, and Fein[19] have recorded a syndrome characterized by clouding of consciousness, cog-wheel rigidities of the extremities, and uncontrollable sucking and grasping reflexes occurring predominantly in persons chronically addicted to alcohol. Since they instituted treatment with hydration and nicotinic acid they note the reduction of mortality from almost invariable death to 15 per cent in this group.

A comparative clinical picture is not seen in endemic pellagrins. Our experience with patients suffering from "alcoholic encephalopathy"[20,21] indicates that they may improve somewhat with the administration of the vitamin B complex. Usually these persons are so ill that one does not care to risk waiting to see if they would recover spontaneously. All syndromes associated with alcohol addiction tend to improve with the withdrawal of alcohol, and to continue to improve until alcohol again is ingested.

*Wernicke Syndrome:*The Wernicke syndrome which in most cases is constituted of ophthalmoplegia, polyneuritis, changing levels of consciousness, and mental abnormality, is usually seen in patients addicted to alcohol. It is a non-specific reaction. It has been thought that it may be the result of nutritional deficiency.[22] Alexander[23] noted the production of a disease in pigeons by feeding a diet deficient in thiamine, which had as a basis pathologic changes comparable to those observed in persons dying with Wernicke's syndrome. These lesions usually are confined to the periventricular gray matter and are characterized by varicose deformities of the blood vessels and hemorrhage and necrosis in the adjoining parenchyma. Most constantly involved are the paramedian and paraventricular nuclei of the thalamus and hypothalamus, the mammillary bodies, the nuclei of the third, fourth, sixth, and tenth nerves (dorsal nucleus), the nucleus triangularis, and Bechterew's nucleus.

Our experience with the vitamin therapy of the Wernicke syndrome may be illustrated by case reports, which are not selected but represent the most recent cases that have come to our attention. The first patient was closely studied by Doctor John Romano, who has furnished the abstract of her record.

Case 2. A 28 year old woman had been addicted to alcohol for more than five years. Two months before entry to the hospital she developed pain in the calves and burning feet. Three days before entry she became acutely disturbed after a drinking bout. She was tremulous, overactive, disoriented, had sense deceptions, and then fell into stupor. The admission examination revealed stupor from which she could be aroused, mumbling, a poverty of voluntary activity and aimless movements of the extremities when she did arouse, some resistance of the extremities to passive movement, and hyperactive deep reflexes. The eyes could be moved only slightly, and their movements were not coördinated. She developed delirium on the second hospital day, and a Korsakoff psychosis on the third. By the fifth hospital day, the eye movement had improved to such an extent that it was considered to be normal. She had received no nourishment besides parenteral fluid, and parenteral glucose up to that time. She had recovered completely from the psychosis on the sixteenth hospital day, although she had been given no supplemental vitamin products, and had ingested nothing besides the hospital diet. The electroencephalogram which was obtained about every fourth day was grossly abnormal during the early period of her hospital course, improved gradually, and was considered to be normal on the twenty-fifth hospital day. Although she had not received any nutrition besides the hospital diet, she appeared entirely normal and returned to work.

This course of events represents remarkable recovery from the Wernicke syndrome in a young woman chronically addicted to alcohol, the recovery occurring in the face of no therapy other than withdrawal of alcohol, sedation, rest in bed, and the parenteral administration of water and glucose solution. This experience would appear to indicate that the ingestion of alcohol over a long period may be a cause of the Wernicke syndrome.

Case 3. A 32 year old colored female, an alcohol addict of indeterminate standing (many years) was thought to be all right during her rare sober movements, until the morning of admission to the hospital when examination revealed stupor, slurred speech, and disorientation. The eyes could not be elevated or depressed. The left eye could be moved slightly medially and laterally, the right eye deviated slightly downward on lateral rotation which was rather adequate. Medial movement of the right eye was efficient. She could not converge the eyes and there was bilateral ptosis. She had a Korsakoff psychosis and a mild peripheral neuritis. The lateral eye movements improved spontaneously on the fourth hospital day. Thereafter besides the hospital diet, she was given 200 mg. nicotinic acid daily in broken doses, an ounce of brewer's yeast three times a day, and thiamine 50 mg. intravenously for three days followed by 5 mg. three times a day by mouth. This vitamin therapy was continued in the hospital for thirty days without affecting either the remaining signs of the Wernicke syndrome or the psychosis. Three months later while still taking an ounce of brewer's yeast twice a day she remains unable to move the eyes up or down or to converge them; the psychosis is unimproved. She is again drinking heavily.

This experience would appear to indicate that the Wernicke syndrome may not improve over a period of thirty days and longer, with copious administration of certain vitamins of the B complex.

Case 4. A 50 year old white man noticed fatigue and increasing weakness four months before his admission to the Cincinnati General Hospital. He lost his appetite and had several bouts of vomiting. These symptoms had progressed in severity until

four days before hospital entry when he had to take to bed. On the third day he developed diplopia, strabismus, vertigo, unsteadiness, and he himself noted that he couldn't cerebrate normally. The feet and legs developed numbness and tingling, and the tongue was sore at the tip. The patient had had gastric symptoms for longer than 15 years; he had been a heavy imbiber of alcohol up to five or six years ago. His dietary had been restricted for years. The admission examination revealed considerable unsteadiness, the patient would not sit because of it, preferring the recumbent posture. Memory for recent events was poor, he confabulated and expressed a few paranoid ideas. The eyes rested at the inner canthi ("crossed"), and there was gross nystagmus when he attempted to move them. There were signs of mild peripheral neuritis in the lower extremities. All movements of the extremities were unsteady. The tongue was swollen, fiery red, and the papillae smooth. There was no skin eruption.

On the day of admission to the hospital he was given 3 ounces of brewer's yeast and 50 mg. cevitamic acid; and 100 mg. of thiamine parenterally in four doses of 25 mg. each. The strabismus and neuritis remitted promptly, but he developed considerable delirium and then the Korsakoff psychosis. Niacin amide was then administered in 100 mg. doses every hour. The severe psychotic symptoms remitted after he had received 1000 mg. of this substance. He promptly sat up in bed, read the paper, and appeared to be rational. Recent memory defect remained as did the nystagmus.

This experience would appear to indicate that the Wernicke syndrome may result from nutritional deprivation. The psychosis was considered to be an accompaniment of pellagra, which was the diagnosis in this patient, since it responded with such speed to niacin.

Case 5. A 63 year old white woman had had episodes of vomiting monthly for 17 years. They had become more frequent as time passed until they occurred practically after each meal for the week before admission to the hospital. For three months there had been ringing and buzzing in both ears, since then she had gradually lost her hearing until she became completely deaf. She had complained of boring, occipital headache for several months. For one week before admission she had not talked much. Five days before entry she took to her bed. Two days later she became incontinent of urine and feces, and had auditory hallucinations and complete loss of recent memory. Mild psychic signs (confusion, memory loss) had been present for two months. Two days before admission she ceased eating, had jerking movements of the eyes, and was drowsy.

On the admission examination she was somnolent but not stuporous; she waked up readily to coöperate, the tongue was smooth, the heart was enlarged, the blood pressure was 140/90 and there was pitting edema of the lower extremities. The skin of the legs was extremely thick and corrugated and contained patches of discolored scaling (chronic edema). The abnormal neurological findings were an inability to move the eyes upward or downward more than infinitesimally, and convergence of the eyes was impossible. She had difficulty maintaining lateral deviation of the eyes, which was accompanied by coarse nystagmus. Nystagmus was seen with the eyes in a neutral position, at rest. There was moderate bilateral ptosis. There was complete bilateral deafness. She could not bear a tuning fork placed anywhere on the skull. One could obtain coöperation with mimicry; she could not hear shouted requests. She was mildly and generally weak. She did not tolerate applicator stroke in the lower extremities because of the pain it caused. Further sensory tests were not attempted. No tendon reflexes were obtained in the legs and the plantar responses were bilaterally extensor in type. She had sucking and snout reflexes, but a normal jaw jerk, and no Hoffmanns.

Because of the severe involvement of the eye movements (the upward and downward movement of the eyes was reminiscent of limited skew deviation), the bilateral deafness and bilateral pyramidal tract signs, she was considered to have a tumor im-

pinging on the quadrigeminal plate. The similarity of her findings to those of pineal tumor were discussed, and the possibility of the Wernicke syndrome was mentioned.

Because her condition was somewhat urgent she was given 50 mg. of thiamine and 100 mg. of niacin by mouth daily for four days, then 50 mg. of thiamine intravenously twice a day for three days. On the second hospital day, 24 hours after vitamin therapy was begun she was able to move her eyes better in the vertical plane. The eye movements continued to improve until they were of normal excursion on the fourth hospital day. At this time the oral administration of vitamins was supplanted by the intravenous injection of 50 mg. of thiamine twice daily for three days. She was alert within 24 hours after the initiation of parenteral therapy, but it was now not difficult to elicit the signs of a Korsakoff psychosis and moderately severe peripheral neuritis. The day after the intravenous therapy was begun, she could hear the slightly raised voice. An audiogram done on the seventh hospital day revealed a 55 per cent loss of hearing in either ear. She has continued to have the signs of severe mental deterioration which were immediately demonstrable on her spontaneous arousing from stupor on the fifth hospital day. Her hearing had continued to improve slightly. We are at present supplementing the hospital diet with 5 mg. of thiamine three times daily, and 100 mg. niacin amide six times daily.

A thorough history in this case was available from the daughter, who lived with the patient. She had drunk two to three quarts of beer daily for about thirty years, using it in place of water. She took no strong alcoholic beverages. The patient was something of a food faddist. She ate practically no meat, eggs, cheese, or butter. She ate sparingly of bread. She drank considerable sweet milk, chocolate milk, and buttermilk. She had gradually reduced her food intake over the past year and for about nine months had eaten little, subsisting chiefly on liquids.

The dramatic improvement in hearing from total deafness is noteworthy particularly in light of Selfridge's[24] report of quantitative improvement in hearing with niacin administration. We had noticed some slight improvement in the hearing of some pellagrins receiving vitamin B complex but had thought that it was due to increased alertness.

It is possible that this patient's improvement would have occurred spontaneously, and the same may be said of Case 4.

It is apparent that in man at least, the Wernicke syndrome may be associated with prolonged alcoholism or with undoubted nutritional deficiency. In our experience the former is the more frequent. The Wernicke syndrome is not a frequent occurrence in any case; in the Nutrition Clinic at Birmingham its occurrence has been observed possibly twice in over 2,000 cases of nutritional deficiency. The term possibly is used since the diagnosis was uncertain in one case (Aring et al,[10] Case 3). The patient was a 45 year old woman who had had the first attack of pellagra in 1925. She drank no alcohol. She had suffered an old injury to the right eye at the age of 10 which had resulted in blindness, and abnormal pupillary reaction in this eye as well as external strabismus. No lens was present in this eye and there was a membranous secondary cataract, hippus, and posterior synechiae. The signs which might

have been considered as part of the Wernicke syndrome were partial bilateral ptosis, and considerable limitation of upward gaze. Neither of these signs improved after the use of much Vitamin B_1 administered parenterally and orally.

It may be surmised from these case reports that a patient may make a spectacular recovery from the eye signs of the Wernicke syndrome with vitamin therapy, that he may recover apparently spontaneously, or that he may make no improvement despite vitamin therapy. The latter experience has not been uncommon at the Cincinnati General Hospital. We may predicate reversibility and irreversibility without saying anything.

The alert physician who sees this syndrome will try vitamin therapy parenterally at first, but he will not promise too much and thence will not have to retract, or be forced to see things which do not exist. It is unusual for the evidence of associated mental deterioration to clear with the administration of vitamin B.

Korsakoff Psychosis: This non-specific syndrome is characterized by disorientation, memory defect with difficulty in retention and recall, and confabulation. It may be associated with peripheral neuritis. It usually runs a chronic course with permanent mental changes. The Korsakoff psychosis does not respond to the administration of vitamins.

Delirium Tremens: The course of delirium tremens is not altered by vitamins.[25] After reviewing the literature of the late eighteenth and early nineteenth century, Romano[26] noted that the prognosis then as now was good in delirium tremens if alcohol was withdrawn and a sedative administered. He concluded that no improvement had been made in the rational treatment of delirium tremens in over a century with the exception of the boon of paraldehyde and a wider awareness of the psychological factors of the disorder.

Migraine: I have had no experience with the use of vitamin B in migraine. It has been noted that good results may be obtained with an average monthly dose of 350 to 450 mg. of thiamine given parenterally, with initial injections of 30 to 90 mg. given daily. The frequency of injection was reduced over a period of about three months. If no favorable result was obtained in four weeks, 15 U.S.P. units of liver extract were administered parenterally once or twice a week. To terminate a migraine attack 60 to 120 mg. of thiamine were given intravenously or intramuscularly.

It is unusual that such prolonged vitamin therapy is necessary in an active disease. Those cases of migraine noted by Palmer[27] were of extreme severity as far as pain and frequency of attack were concerned. It has been the experience of those working with vitamins that efficacy is obtained quickly if it is to be had. Another oddity about the migraine patients which Palmer has observed, in addition to those treated with vitamins, is the comparatively low incidence of benefit (58.8 per cent) obtained from the use of ergotamine tartrate.

The Lesser Members of the B Complex from a Neurological Standpoint: Riboflavin deficiency has not been found to produce neurological symptoms, although it may manifest its association by inflammation of the lips, the formation of fissures at the angles of the mouth, glossitis, dermatitis, and vascularizing keratitis.

Paraminobenzoic acid, pantothenic acid, inositol, and choline have been used in neuritis and subacute combined system disease in man usually without effect. Since a lack of pantothenic acid and pyridoxine in the diet of pigs is associated with abnormal gait, degenerative changes in the peripheral nerves, posterior root ganglia and posterior columns of the cord,[28] these substances need further evaluation in human deficiency disease.

Adenylic acid is present in high concentration in yeast and crude liver extracts, and like thiamine and niacin, is an organic catalyst essential for cell respiration. Because of the suggested relationship of adenylic acid and vitamins of the B complex, it might be of importance in nutrition. There is some evidence[29] that it may be of use in the therapy of nutritional deficiency neuritis.

Quiescent Brain Lesion Unmasked by Thiamine Deficiency: The work of Odom and McEachern[30] appears to be of considerable importance, and it should be repeated promptly in the various species. These investigators placed cats with old surgical brain scars on a thiamine deficient diet. These animals showed no clinical evidence of neurological deficit until it was unmasked by vitamin deficiency. Then signs referable to the portion of the brain damaged made their appearance, and regressed promptly with the parenteral injection of thiamine.

The unmasking of brain deficit is of peculiar importance to neurologists. If one may speculate in another species from these results, they may explain the reported relief of some neurological symptoms in man which are not the direct result of nutritional deficiency. It should

be remembered that there is considerable bilateral representation of function in the hemisphere of the cat. If all tissue is dependent for health on thiamine, presumably a defect in one cerebral hemisphere might manifest itself by the decompensation that is occurring in the opposite healthier hemisphere, which under ordinary circumstances was able to cover the deficit. We know relatively little about the mechanism for compensation in hemiplegic deficit. Presumably in the case of cats, transhemispheral connections are susceptible to thiamine deficiency. One awaits the pathological studies in their cats.

The work of Odom and McEachern supports the concept of irreversibility in nutritional deficiency, since animals whose deficiency was remedied with ease during their first episode of deficiency, were not so readily relieved after a second episode. In cats undergoing thiamine depletion more than a single time, improvement occurred much more slowly and some residual weakness and incoördination remained despite repeated daily injections of thiamine. Repeated thiamine depletion frequently resulted in death.

General Considerations: There are a few simple concepts about the use of the vitamin B complex, the only vitamin which is of much use in neurological disease. Whether the disease is the result of a primary nutritional deficiency, or a neurological disease unmasked by a secondary deficiency, the response to vitamin B complex therapy if it is to occur, occurs promptly (usually one to two days, sometimes three to seven days). These vitamins should be administered in large doses parenterally (thiamine 25 mg. three times a day; nicotinic acid 100 mg. six times a day; nicotinic acid amide, if no vasodilatation is desired, 100 mg. six times a day; vitamin B_6 50 mg. twice a day) in the early days of the therapy. There is no convincing evidence that one can overdose with these substances, although a financial overdose to the patient should be a consideration. When the desired result is initiated oral therapy may be resorted to, expecting improvement to continue with maintenance dosages if absorption is normal (thiamine 1½ to 2 mg. daily, nicotinic acid amide 15 to 20 mg. daily, vitamin B_6 (pyridoxine) dosage unknown). Physicians should familiarize themselves with what is considered to be a generous, well-balanced diet[31] for which a few vitamins are not a substitute.

Since the evidence indicates that favorable clinical and experimental response is prompt to vitamin therapy, it follows that advice urging

that patients be saturated with vitamins for months before results can be expected should be examined with considerable criticism. Even if the disease be of the so-called irreversible type, it seems futile to pour the vitamins into the body for a prolonged period, particularly when the patient apparently is ingesting an adequate diet.[14] The therapeutic test should not be withheld, but there appear to be quite definite limits to its significant duration. The nutritious diet should never be lost sight of.

Certain pharmacological properties that might evolve on the use of the vitamins should be considered, since such effects may have nothing to do with nutritional deficiency. Thus niacin is a potent peripheral and cerebral vasodilator[32,33] and might conceivably be effective wherever vasodilatation is beneficial. The use of niacin in trigeminal neuralgia[34] is based on its property of vasodilatation. Niacin amide does not cause vasodilatation.

The factor of deprivation of several nutritional elements should be stressed in neurological disease due to malnutrition. Therefore the administration of a single vitamin in the therapy of these conditions is not a sound procedure. The best method of administering a number of vitamins parenterally is to give liver extract intramuscularly. The maintenance dose of this substance in subacute combined degeneration of the spinal cord under control is 15 U.S.P. units of purified liver every four weeks, which might be used somewhat as a guide in cases of nutritional deficiency. The dose should be graded upward to coincide with the severity and acuteness of the illness. In any case the oral or parenteral use of vitamins is not a happy substitute for the generous, nutritious diet.

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SPEECH DISORDERS AND THEIR TREATMENT*

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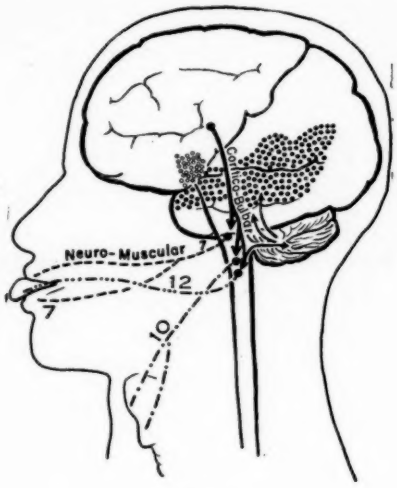
IN order to understand speech disorders, one must know something of the development of speech in man and his ancestors. In phylogeny there is evident a close relationship between the development of binocular vision, manual skill, and finally a leading hand and leading cerebral hemisphere. When man's shrew-like ancestors took to trees and left behind them quadrupedal locomotion, their fore-limbs were emancipated to become hands, and the possibility of dexterity developed. Other vertebrates specialize and reach narrow superiority by unique development of one type of sense organ. Man excels because of lack of specialization. His speciality is a leading hemisphere, evenly developed in the reception and elaboration of all types of sensory impression. It is this even development that allows for association between the different sensory receiving stations; and it is the development of the mechanism of association that has made intellectual behavior possible. The dominance of the left hemisphere is marked in right-handed people, who constitute about 75 per cent of the population. The functions are probably not confined to the left hemisphere; the dominance is relative. Recent studies have shown that even speech is subserved in a rudimentary way in the right hemisphere of right-handed persons. With a leading hemisphere in which there is a predominant centering of manual skill (eupraxia), symbolic understanding (eugnosia), and language, there is a great need of many associative tracts. The function of language needs both eupraxia and eugnosia, in fact, each needs the other two for effective behavior. Nevertheless it can be taken as a proposition that language is the most highly integrated of man's functions.[1,2,3]

In the central nervous system of man, speech is integrated at five important levels; these are not exact, and to some extent overlap but for purposes of exposition Fig. 1 shows the main centers involved. The

* Given October 20, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine.



V—Social, Personal, Emotional, etc.

IV—Symbolic, Inter-personal

III—Cerebellar

II—Cortico-bulbar

I—Neuro-muscular

Fig. 1

broken lines show the lowest level, the neuron from a nucleus in the medulla (seventh, tenth or twelfth) to a peripheral organ of speech, lips, tongue or larynx. This is level I, the neuromuscular neurons and the final common paths over which all nerve impulses concerned with speech must pass. Level II is the neuron arising in the motor cortex and ending in the medulla around the bulbar nuclei (seventh, tenth and twelfth), its fibers pass down the corona radiata, through the internal capsule to the peduncles and medulla. This, too, is a common pathway for all the complex speech integrations of the higher levels. It is closely correlated for motor speech production with the cerebellar paths (Level III) which run up from the medulla to the cerebellar cortex, thence to cerebellar efferent nuclei and upward to mid-brain, thalamus and motor cortex. This makes a loop and supplies the mechanism of coördination so greatly needed in the control of speech. These three levels can be considered together as a rather straightforward motor mechanism.

Moving up to Level IV is a big step, for symbolization and meaning come in here. The anatomical localization is cortical with intricate association fibers between the different parts of the speech areas (dotted on cortex of Fig. 1). The circular stippling indicates the motor speech area (Broca), the black stipples show the auditory and visual areas of langu-

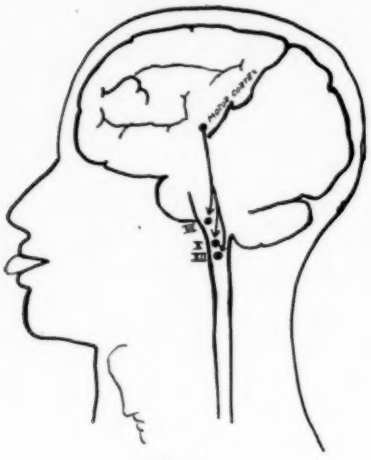


Fig. 2

LEVEL II—CORTICO-BULBAR

Common Lesions: Syphilis (G.P.I.), Cerebral Arteriosclerosis

Clinical Results: Dysarthria, Weakness, Paresis or Partial Paralysis

Treatment: Antiluetic or none

age functions and their subsidiaries. These areas are well developed in only one hemisphere, the "leading hemisphere," usually the left. The degree of dominance is important.

Level V is the most highly integrated and least localizable. It is associated with the great association area of the frontal and parietal lobes. It brings in memories, individual life experiences and the impact of one person upon another including the varied and important emotional reactions expressed by glands, smooth muscle and skeletal muscle. The visceral expressions are mediated by the hypothalamus and the autonomic system; the overt behavior responses are expressed largely by skeletal muscles as behavior. Although both may *express* emotions, they are not the *sources* of emotion, which must be looked upon as largely cortical, individual and extremely complex.

Taking up each level in turn in regard to (a) common lesions, (b) clinical results of these lesions, and (c) treatment, one finds little of interest in level I. The lesions are usually the obvious developmental defects of the end organs treated by surgery, e.g., hare-lip and cleft palate. Tying down of the tongue by a short frenulum is emphasized by some but is actually a rarity. Trauma and neuritis may paralyze the nerves. Surgical anastomosis may be necessary. Poliomyelitis or more rare degenerative diseases may cause nuclear lesions and, hence, bulbar

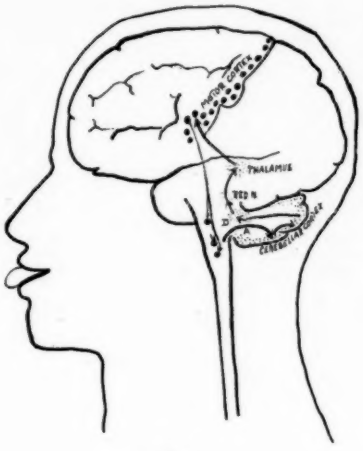


Fig. 3

LEVEL III—CEREBELLAR

Common Lesions: Multiple Sclerosis, Tumor, Encephalitis

Clinical Results: Incoordinate Speech, Scanning, Monotonous, Flat, Explosive, Staccato, etc.

Treatment: Possible Removal of Tumor; Usually None

palsy. Treatment is unsatisfactory; excessive doses of vitamins may be tried.

At Level II the cortico-bulbar neurons are found to be frequently affected by syphilis, as in dementia paralytica ("G.P.I.") and by cortical softenings from arteriosclerosis. Other pathological processes, such as tumor or encephalitis lethargica, rarely damage these neurons in a selective way. The result of injury to the nerve cells of the motor area which innervate bulbar speech mechanism is weakness, partial paralysis. It is partial because the innervation is bilateral, neurons from one motor area going to the nuclei on both sides of the medulla, although, predominantly to the opposite side. The clinical symptom produced by this weakness is *dysarthria* or slurred speech. The classical example is the patient with "G.P.I." who cannot enunciate "Methodist episcopal" but says something like "Methyst epistople." The treatment of this sort of bad enunciation is unsatisfactory. Antiluetic treatment sometimes brings back paretics' poor speech. Usually little or nothing can be done. The slovenly speech of uneducated persons must be ruled out by repeated trials of different test phrases and attention to other clinical symptoms.

The third level (III in Fig. 1) is elaborated in Fig. 3 to show more details of the cerebellar coördinating mechanism. Nerve impulses from cells in the medulla enter the cerebellum over afferent tracts (A) bringing in proprioceptive information, data as to what the muscles are doing.

This is spread through the cerebellar cortex by the plentiful association fibers. Impulses then leave the cortex of the cerebellum and go to dentate nucleus (D) whence they are relayed upward through the red nucleus to the thalamus. From here another neuron takes them to the motor cortex of the cerebrum where they have their effect on the motor impulses sent out from headquarters. Impulses from the roof nuclei of the cerebellum and from the red nucleus probably go directly down to brainstem and spinal centers to effect further motor control. Thus a loop or series of loops, is formed for making the delicate motor adjustments of speech all work together. The mechanism is for coördination or synergia.

Lesions anywhere along this pathway will cause trouble. The commonest to disrupt smooth speech are those of multiple sclerosis and epidemic encephalitis; tumors and softenings may also do the same. The clinical results are incoördination (asynergia) of speech, shown in the monotonous speech of Parkinson's disease (where the lesion is probably up near the thalamus), in the scanning speech of multiple sclerosis, and in the various explosive and staccato forms of speech found in encephalitis. Except for the rare removal of tumors, treatment is of no avail.

Level IV is divided in two parts (a) and (b) because (a) takes in the functions of the dominant, leading hemisphere, those functions which are largely absent in the minor hemisphere, while (b) is the relationship between the leading and minor hemispheres. It deals with the degree of dominance of one over the other.

Level IVa (Fig. 4) is concerned with symbolism. Symbols must be sensed, recognized and understood as meaning something. The senses important to language are vision and hearing, each has three levels of integration. Visual reception is localized in the occipital pole and visual recognition in the stippled area just anterior to this. A lesion at the first level causes blindness; at the second, loss of recognition of perceived objects, in other words, visual agnosia. A lesion farther forward, but still behind the angular gyrus (LEX Fig. 4) causes visual disorientation. The patient cannot remember the plan of a house, or he gets lost, although he may recognize the street or house he is seeing at the moment, because he cannot bring back series of pictures.

The auditory sense has three similar levels in the temporal lobe: auditory reception (AUD. REC., Fig. 4), auditory recognition of noises

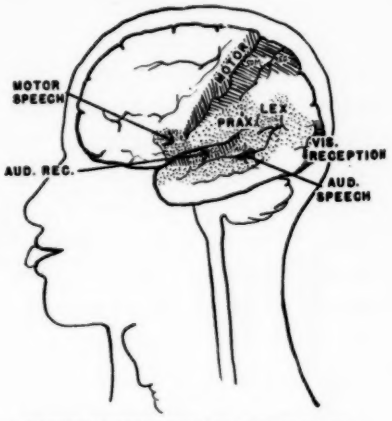


Fig. 4

LEVEL IVa—SYMBOLIC

Common Lesions: Arteriosclerotic Softening, Tumor and Trauma

Clinical Results: Deafness and Blindness, Apraxia and Motor Aphasia, Visual and Vis. Verbal Agnosia, Auditory and Aud. Verbal Agnosia, Agraphia, Amusia, Acalculia, etc., Semantic and Amnesic Aphasia

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LEVEL IVb—LATERAL DOMINANCE

Common Lesion: Unknown, Inherited

Clinical Result: Slow Reading, Reversals, etc., Stammering, Ambidexterity

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Treatment: Retraining by Reading, Speaking, Writing, etc. (Orton)

and auditory recognition of symbols (words). Since the innervation of the temporal lobe is bilateral, a single cerebral lesion does not necessarily cause complete agnosia, and only bilateral lesions can cause deafness. Acoustic agnosia for sounds is not known to occur without some acoustic verbal agnosia, but in many cases of the latter the recognition for sounds is retained. Thus it is obvious that the acoustic mechanism is more variable and less unilaterally dominant than the visual mechanism. Recognition of learned symbols for words seen is in the angular gyrus, (LEX Fig. 4), and a lesion here causes visual verbal agnosia. The patient cannot read, he has "alexia" or "word blindness," as opposed to the "word deafness" resulting from a lesion in the temporal lobe.

Motor dysphasia* is equally complex and depends on an understanding of the fact that no learned motor skill can be practiced without an ideational plan. This is a psychic elaboration necessary as a precursor to the carrying out of any complex motor act. This ideational planning is called eupraxia; the normal person knows how to do a thing quickly and almost automatically when requested. A defect of such performance in response to command is apraxia. It is a symptom of injury to the sensorimotor elaboration areas of the cortex, corresponding to

* Dysphasia, meaning disturbed language, is more accurate in most cases than aphasia, which means lack of language.

agnosia from a lesion in the more strictly sensory area. In relation to most performances eupraxia is bilateral, the acts of one hand, for example, being planned in the opposite precentral and supramarginal gyri (between PRAX and LEX, Fig. 4). Lesions of these areas or their fiber connections may cause dyspraxia or apraxia.

Apraxia of the organs of speech (tongue, lips, larynx) causes "motor aphasia"; the patient loses the memory of how to make the movements to articulate words; he may know just what he wants to say, but he cannot get the plan of the word into his mind. A lesion of Broca's area (MOTOR SPEECH, Fig. 4) causes this symptom. As a rule only propositional speech is lost when the major motor speech area is injured. This is because the function of language is largely, but not entirely, concentrated in the leading hemisphere; a primitive sort of speech (emotional, expletive, habitual) is subserved in the homologous areas of the minor hemisphere. Individual variation in relation to the degree of handedness is important.

The angular gyrus has the function of symbolic visual recognition, i.e., understanding letters and words by sight. Because words were first learned by hearing, however, this area cannot function if cut off from the temporal lobe. During the process of learning to read, words are sounded out or told to one. Thus the portion of the temporal lobe lying behind "Aud. Speech" (Fig. 4) is of great importance. A lesion here may cause as much loss of reading ability (alexia) as a lesion directly in the angular gyrus. Moreover, because language is learned by associating vision and hearing with objects and symbols, this area is particularly important, Nielsen[4] calls it "the language formation area." Take, for example, the case of objective nouns, the simplest and commonest words used. They are names, usually of objects seen. So memories must be stored in the posterior temporal lobe correlating both visual and auditory meanings. That this is true is shown by cases of temporal lobectomy in which the language formation area of the leading hemisphere is removed. The result is amnesic aphasia. The patient has lost the storage mechanism for nouns; his "naming center" is gone. When shown a pen, he uses circumlocution and may reply "It's to write with" but cannot say "pen."

If one takes these main symptoms (which are well explained physiologically), agnosia, motor aphasia and amnesic aphasia, and adds the obvious complications, it is seen that many special sorts of aphasia are

possible. But by sticking to the principles laid down, these strange phenomena can largely be explained and localized. For example, one can hear music as well as words; therefore "amusia" is found. One can learn several languages and have marked aphasia in one but little in another. Symbols used for mathematics are different from letters; so one may have agnosia for figures. In fact, loss of the ability to calculate is found after lesions in various areas. Semantic aphasia should be mentioned because it is the commonest of all aphasias and is not localizable. It consists of a quantitative reduction in the capacity for and comprehension of speech. The victim has a little of all language functions left but cannot put sentences together or express any complex idea. This phenomenon is present in persons with diffuse cerebral lesions, commonly senile, in toxic patients and in normal but excessively fatigued persons. In fact, almost all patients with aphasia have an element of the semantic form, and careful examination will usually show some mental loss. Semantic aphasia is a form of dementia.

The lesions causing dysphasia and dyspraxia are varied, the commonest being trauma, tumor and softening. Treatment is often not pushed as much as it ought to be. When the first shock of the lesion or operation is over, and the patient is comfortable, re-education should be started. First comes accurate diagnosis,* because the physician must first find out what parts of the language mechanism remain intact in order that he may work on and through these normal or less injured parts. Of course it is equally important to learn how much language the patient had before his cerebral lesion. Was he a laborer with a vocabulary of only a couple of thousand words in one language? Was he a waiter with glib use of five languages, or perhaps a college professor with many thousands of words in two or three languages? The diagnosis and prognosis differ in each case.

Having discovered what sort of a person one has to deal with and what is left of the cerebral speech mechanism, one can outline treatment. If the aphasia is complete there is little to do but to stimulate the patient to more activity and more contact with environment by moving about and occupational therapy. As speech begins to return a place may be found for the entering wedge of treatment. If the case is one of dysphasia ingenuity must be used to make up exercises which will be understood and will re-educate injured cerebral areas or educate the

* The best short method is that of Cheser, E. C., *Bull. Neurol. Inst. New York*, 1937, *6*: 134.

unused area in the minor hemisphere. The evidence is fairly good that the latter is what probably takes place.

For example a patient with visual agnosia cannot recognize objects by sight; he must be shown objects and then be given the cue as to what they are by touch and sound. He looks at the object, feels it and hears the name all at once, and repeatedly. If he has a motor dysphasia with agraphia he is taught to write with his left hand from copy and from dictation. Also he practices speaking words by naming objects while writing the name. The training work is best done by non-medical teachers who have learned the methods in general and who have had from the neurologist special instruction for each case. Goldstein[5] in his recent book shows how varied are the problems and how ingenious the physician must be in planning the therapeutic attack. It is certain, however, that much can be done, especially in young and middle aged people. The teacher must be patient, go slowly and not work long at any one session. A few minutes often tires the patient.

There will be many cases of dysphasia among the many soldiers with head wounds. The specialists in this line of treatment are few and they should begin now to train assistants and teachers to carry out the re-educational procedures. Moreover, many old people with vascular lesions of the brain would be benefited by these methods of treatment, yet most of them are looked upon as hopeless.

Level IVb is actually the same level of structure and integration as IVa, but it deals not only with the function of the dominant hemisphere, but with the relative dominance of the two. Which is dominant and to what extent? In other words there is no 100 per cent use of one and 0 of the other; most persons are very largely right- or left-handed, but 10 or 15 per cent of the population are ambidextrous, have no clear dominance and thus have a lack of leadership in the initiation of speech, writing and reading. There is a mixed lead. One result may be hesitant speech and stuttering; another may be reversed symbols and "strephosymbolia" as described by Orton[6] where letter symbols are confused when similarly formed but differently oriented, as "d" and "b," or words such as "was" and "saw." The left-handed child would like to read from right to left but unfortunately in a right-handed world the books are not printed that way. Uncertainty of dominance is much more common in infants than later in life when habit has settled the question. In other words a *tendency* to right or left handedness is inher-

ited and is only consolidated by habitual use of one side as a leader. In spite of the fact that handedness is inherited, and therefore dependent upon the structure of the genes, no difference can be seen grossly or microscopically between the right and left hemispheres of the brain.

Physiologically it is obvious that one hemisphere leads in normal persons, but lack of clear dominance occurs often. Clinical evidence is impressive that this mechanism of "mixed leads" causes speech and reading defects. Final proof seems to have come from the laboratory, where Lindsley[7] made electroencephalograms of normal people and stammerers during speech. In normals the alpha rhythm of the brain waves was usually synchronous and smooth. In the stammerers the waves in the tracings from the two hemispheres were frequently out of phase and often obliterated, especially when blocking in speech was observed clinically.

Orton's method of training,[6] aimed at making the patient fix his lead in a chosen hemisphere, is an advance in therapy. One must not, however, think that every ambidextrous child will have difficulty in symbolization; perhaps 10 per cent of the population is somewhat ambidextrous and only about one per cent have difficulty. It is probable that ordinary childhood development takes care of most of the cases; habit and use cure the defect; the child "outgrows" his slight disorder. In the cases where the trouble becomes worse and lasts into adolescence and adult life, to become a real disability, one must look for additional causal factors (see level V).

From the standpoint of treatment, it would seem wise to let a left-handed child work out his own salvation. Do not force him to be right-handed in any way; the world will do that gradually because it is a right-handed world the child is born into. The ambidextrous child needs more care; probably he will choose his lead at an early age and follow it, but if reading or speech difficulty develops, he will need visual, auditory and proprioceptive training along Orton's lines to make one hemisphere (preferably the left) clearly dominant. The great desideratum is to accomplish the training with as little emotional stress as possible. Let it be simple and matter of fact. Rather than make it seem too important to the child, give it up, keep the home placid, and wait till the child wants help.

At level V is the highest cerebral complexity of integration. Here associations are somehow stored and conditioned, so that they are indi-

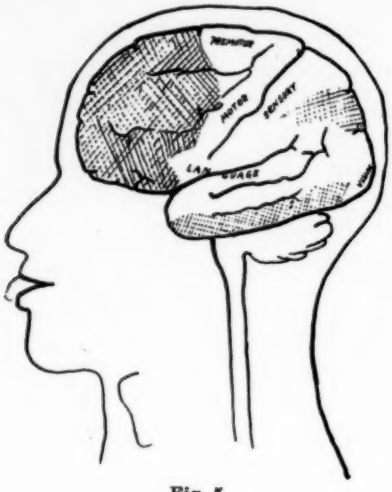

Fig. 5

Level V—Social, Personal, Emotional

Common Lesions: None, or Hereditary

Clinical Results: Stammering, Stuttering, Anxiety, Psychoneurosis

Treatment: Ease Tension, Get Relaxation, Restore Confidence—suggestion, group work, accomplishment; Psychiatric talks, Psychoanalysis, Social Service

vidual, depend on past experience and when summed up constitute personality. The areas involved are shown in Fig. 5. These are the obverse of Fig. 4, which maps out all the specialized areas. What is left over is shaded in Fig. 5, and represents what one supposes, on fairly good evidence, to be the association areas, practically blank in infancy and loaded with personal experience in adulthood. These are the parts of the brain that permit the effect of one person upon another to register and effect character. This associative mechanism allows socialization to take place.[2] When the environment is difficult it is this level of cerebral function that is first affected.

When put under unusual emotional stress, almost anyone stammers. Stammerers are people who habitually hesitate and stick in their speech under stress, but who can talk or read with little hesitation when alone and relaxed. The trouble does not seem to be with the organs of speech, they function well enough when the patient is alone; the essential trouble seems to be in the patient's social relations. He is "shy," cannot "put it over," is afraid to meet people, has varied anxieties and especially has become fearful that he will stammer if called on to speak. Certain sounds are especially difficult, but these vary from month to month and year to year, so it is probable that fear of a certain letter is the cause of the sticking, rather than the sound-formation itself. Any spring board

to start the speech and keep it going, like talking in unison or singing, will get rid of the stammer. Putting the patient on the spot by asking him a direct specific question will bring out the blocking in the speech.

For all these reasons stammering is thought to be a psychoneurosis and there is no doubt of the importance of neurosis as one of the causative agents. Everybody probably has stammered at times. It is the child who connects a *fear* that he will stick next time he tries to speak, who perpetuates the stammering into an anxiety state that may last for years. More complicated neurotic mechanisms are usually behind the fear about speech; the child is neurotically anxious and uses speech as the symptom rather than vomiting, bed-wetting, food fussiness or one of the many other possible neurotic expressions.

Experience in treating stammerers has shown that working on the neurosis and paying no attention to the speech will sometimes cure the stammering. Certainly the results of this procedure are better than giving lessons in elocution, breathing, etc. (which almost always make the patient worse) and better than the trick training methods of some of the stammering schools. The tricks of speech learned often help at first because they are taught with much positive suggestion and confidence is gained by the patient.

Probably the best methods are those that combine psychotherapy, socialization and speech exercise. Blanton[8] has written a good book on this subject. Successful schools that do this well are run by Dr. Green in New York and Mr. Martin at Bristol, R. I. The patients must learn to relax, to speak without spasm, to literally "take it easy." Nothing helps this more than good suggestions, properly and repeatedly employed, and success. The success is the most important thing, it allays fear and builds confidence. Speaking in unison, singing, helping each other, all help the patient to extravert himself and shed his anxiety.

Sometimes one line of treatment alone will effect a cure. Jacobson[9] in Chicago has had success with relaxation exercises alone. A few instances are known where psychoanalysis worked. Hypnosis has cured a few. But these phenomena must be looked at as examples of taking a few straws from the camel's back. If one wants to be sure to help, it is far better to use several methods of attack at the same time—directed against the *fear*, the *spasm*, and the social withdrawal. Inheritance is an important causal factor but nothing can be done about it. For the patient it is best forgotten; for the therapist, it should be constantly kept

mind. Most stammerers probably inherit an inferior speech apparatus (often linked with a left-handed or ambidextrous tendency). This may be harmless unless the social situation and the patient's interpersonal relations precipitate anxiety and fix it into psychoneurosis. The neurosis takes hold of the least resistant system and causes symptoms. The etiology is multiple, and treatment must be varied to match it. The inheritance of a weak speech mechanism is no obligation to stammer. Emphasis in treatment should be put on amelioration not cure, for few are ever entirely relieved of symptoms.

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THE PREVENTION AND TREATMENT OF CONVULSIVE DISORDERS*

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THE subject for our discussion tonight has for a score of centuries been the picnic-ground for a merry-go-round of inconclusive thinking. The twenty-seven different names which have been applied to convulsions and their contradictory connotations are evidence for this statement.

The "Sacred Disease" is opposed by the "Demon Disease"; the "Shining Disease" by the "Black Disease"; "St. Anthony Disease" by the "Filthy Disease." However, non-committal descriptive terms have survived longest, "Commitialis Morbus," "The Falling Sickness," "Epilepsy" and our English, "Fits."

"Paroxysmal Convulsive Disorders," the choice of the American Neurological Association and hence, out of courtesy, my title for this evening, represents an effort to escape the fear and loathing which has encrusted the term "epilepsy" in its passage through the Dark Ages. The effort is commendable but the choice defeats its own purpose. "Convulsive Disorders" centers attention on the convulsion, the most fearful aspect of a seizure. "Disorders of Consciousness" would be a preferable term for two reasons. First, loss or impairment of consciousness is less feared than a convulsion; syncope is commonplace; sleep is an every day, or every night, occurrence. Second, and more important, loss of consciousness is the central sun of the constellation of symptoms which make up a seizure. The seizure most distinctive of epilepsy, both clinically and electrically, is the petit mal, a transient loss of consciousness accompanied by the three-per-second alternate dart-and-dome dysrhythmia. This form of seizure is relatively more common in so-called "essential epilepsy," is not reproducible by artificial means, such as the use of convulsant drugs, and constitutes abou 70 per cent of all seizures. Both consideration for patients and scientific accuracy vote for the

* Read October 23, 1942 in the fifteenth Graduate Fortnight of The New York Academy of Medicine.

term "disorders of consciousness." Objection that there are many forms of unconsciousness can be countered by mention of the many conditions in which involuntary convulsive muscular movements are the presenting symptom—chorea, tetany, habit spasms, eclampsia, hiccup, sneezing, orgasm, and so forth.

Tempering the wind to the shorn lamb is an act of mercy and the physician in speaking to his patient often finds use for wishful words which also conceal: spasmophilia, pyknolepsy, fainting spells, or nervous turns. If we wish to go the whole way in both camouflage and scientific accuracy, the proper expression is "symptomatic cerebral dysrhythmia."[1] However, sugar-coating is neither desirable nor necessary in this medical presence and with your permission, I shall substitute the unpleasantly familiar term "epilepsy" for the multiform "convulsive disorders."

Traditionally, etiological factors have been separated into two distinct groups. First is the so-called "idiopathic" or "cryptogenic epilepsy," seizures out of the nowhere into the here. The word "idiopathic" means "one's own suffering"—a condition, the cause of which is not extrinsic but arises out of one's own peculiar make-up, an inborn characteristic. The terms "idiopathic," "constitutional," and "hereditary" would seem to be interchangeable. In the second group, symptomatic epilepsy, seizures are the result of some pathology of body or brain. The last five years have altered 500-year-old conceptions. Idiopathic epilepsy is no longer a Jovian thunderbolt out of the blue, unpredictable and inscrutable, but is a disturbance in the chemical makeup or reactions of the discharging cells of the brain. This chemical disorder results in a disturbance in the orderly pulsations of the electrical currents of the brain and these electrical pulsations as recorded seem to be a hereditary trait. Studies of the brain-wave records of the epileptic and his relatives bring support to the suggestion that an underlying defect has been transmitted. Epilepsy is a double-headed dragon, but with only one heart, cerebral dysrhythmia, a heart which a daring Saint George M.D. will someday pierce. Instead of the obscure ancient terms "idiopathic" and "symptomatic," I propose the clear-cut terms "genetic" and "acquired."

This terminology has the advantage of placing epilepsy on the same footing as other metabolic diseases. The word "idiopathic" or "cryptogenic" implies an origin which is mysterious, and unknowable, a sort of

spontaneous combustion of devastating symptoms. "Genetic" implies predisposition or more specifically genes and chromosomes and their chemical structures which, if they cannot be seen, can at least be visualized. "Acquired" is entirely distinct from "genetic" and yet the processes are complementary. Modern geneticists emphasize what clinicians have postulated for centuries, namely, that heredity and environment are complementary factors whose joint action produce many of the ills which beset body and brain. Diabetes, hypertension, tuberculosis, obesity, cancer are but examples of scores of disease conditions which are both transmitted and acquired. Seed and soil combine to make a plant; spark and gunpowder, to make an explosion. Although in the great majority of patients both factors are at work, their relative importance varies from patient to patient. Probably the case is rare in which only heredity or only an acquired cause is responsible for seizures. Nevertheless, these two categories are clinically useful, if, when we speak of either genetic or acquired epilepsy, we recognize the probability that acquired or genetic factors respectively are also partially responsible. I stress this point because a comprehensive and effective program of treatment must be based on a recognition of multiple causes in the individual patient.

Prevention: If, as a general rule, "an ounce of prevention is worth a pound of cure," then in epilepsy a milligram of prevention would be worth a kilogram of cure. During the last twenty years I have examined thousands of articles which dealt with the subject of epilepsy but remember only a few which attacked the important subject of prevention. This neglect is due to the fact that a seizure is almost always a complete surprise to all concerned. "We never dreamed," say the parents, "that such a thing could happen to our child." Eighty-three per cent will add, "There has never been a case like this on either side." The doctor examines the patient, pronounces him sound and healthy, and mutters to himself. "Cryptogenic"—born of secrecy—"epilepsy." Having no conception of a cause, he cannot conceive prevention, though he may be able to provide symptomatic treatment.

As I have stated, there are two general causes of seizures, genetic and acquired, and in any given patient the twin influences are at work. However, in three fourths of patients, the genetic forces seem to prevail, and in one-fourth, one or more of the environmental factors. In spite of this preponderance, geneticists warn that even if sterilization of

epileptics were universally applied, benefit to future generations would be negligible, because the vastly more numerous "carriers" transmit the disorder as readily as epileptics but cannot be identified. We are able to stress prevention by means of eugenics only because of the almost telepathic aid given by the electroencephalogram.

This is not the occasion for a presentation of laboratory data but I need to say that Dr. and Mrs. Gibbs and I have made and classified electroencephalograms of 1,000 normal control persons, 1,260 epileptics, 320 near relatives of epileptics, and 80 twins (160 co-twins), identical and non-identical, epileptic and non-epileptic.[2,3,4] Study of these data leads to these conclusions: the pattern of brain waves is an hereditary trait; epilepsy, per se, is not inherited, but a predisposition is, and in most persons this predisposition, if present, is represented as an abnormality in the electroenchephalogram. The brain-wave pattern is not fixed but a fluid trait and various considerations blunt the sharpness of the deductions which can be drawn from it. Nevertheless, this technique seems to make it possible to trace the underground asymptomatic course of epilepsy through the generations, to give advice about marriage and childbearing based on individual rather than on general facts and possibly to take the offensive against epilepsy by starting treatment before the seizures begin.

Thus, the prevention of epilepsy by means of eugenics, requires the dying out or the breeding out of hereditary dysrhythmia. The question of whether transmitted dysrhythmia is a dominant or a recessive, and whether disordered brain waves could be "bred out" by crossing with ordered brain waves, must await the collection of more data and the decision of geneticists. Moreover, given a person whose electroencephalogram is abnormal, we must know that his dysrhythmia is transmitted and not acquired, and we must learn the genetic significance of various degrees and types of abnormality. It would now seem that epilepsy will be the chief beneficiary of this study, for of all neuropsychiatric disorders, dysrhythmia seems to be most consistently present (85 to 90 per cent) in persons subject to seizures. In epileptics the most distinctive abnormality is the intermittent appearance on the electroencephalographic record of short bursts of high-voltage waves which may be abnormally fast, slow, or else alternately fast or slow—what the Gibbs call "seizure-discharges." Records with this type of disturbance are found 33 times more frequently in epileptics and 7.7 times

more frequently in their relatives than in a control population. The corresponding multiples for records without seizure-discharges, but which are grossly slow or fast, are 19 times and 4.8 times. The multiples for records which are only moderately slow or fast are 2.3 and 2.9 times. Pushing the comparison still farther, in epileptics paroxysmal discharges are 13 times more important than moderate slowness or fastness of rate, and in the relatives of epileptics, they are three times more important. The proportion of petit mal patients in the group is influential in studies of this sort, for 86 per cent of patients who have only petit mal have records classed as paroxysmal against 45 per cent of patients who have only psychomotor seizures, and 17 per cent of patients who have only grand mal.[2]

Hereditary dysrhythmia can be prevented only by means of eugenics, either by forbidding progeny to all persons with transmitted and serious brain-wave disorders—an imposing task—or perhaps by dilution of the trait through their marriage with persons possessed of normal brain waves. On the other hand, even if a disordered pattern of brain waves has been inherited, epilepsy itself may possibly be prevented if environmental conditions which act as precipitants of seizures can be avoided. I refer to trauma received at birth or later in life from traffic or industrial accidents or from wounds received in war, certain infections which invade the brain or meninges, encephalitis, meningitis, whooping-cough, and syphilis, certain severe circulatory or emotional disturbances, and many convulsant drugs, the most common of which is alcohol. Prevention of these precipitating conditions lies partly with the public and its elected representatives and partly with the individual.

Finally, whether an observed dysrhythmia is transmitted or acquired there is the possibility of preventing the appearance of clinical manifestations through the use of anticonvulsant drugs in the pre-seizure period. This possibility has not as yet been tested. Obviously, it would be more apropos in children, in persons with definite seizure-discharges, and in those who have a previous history of brain injury or have displayed symptoms which might be premonitory—an infantile convulsion, temper tantrums, enuresis, periods of unexplained sleep, dizziness, falling, head-nodding, and so forth. Without the aid of the electroencephalogram, preventive measures must deal with such relatively indirect matters as better obstetrics, fewer wars, and a clearer recognition of premonitory symptoms.

Treatment: Insofar as treatment is based on etiology, the search for the cause or causes of seizures must be highly individualized. This requires careful history-taking and painstaking examinations. One must attempt to rule out each of the dozens of conditions which, if present, act as contributing causes for convulsions. Most prominent of these conditions are congenital maldevelopments, birth or later brain trauma, brain or meningeal infections, intracranial tumors, circulatory lesions, severe metabolic or endocrine abnormalities, toxemias, convulsant drugs, and borderline states simulating epilepsy. These latter embrace syncope, irritable carotid sinus, vasovagal seizures, hysteria, and eclampsia. A shrewd guess as to the presence or absence of one of these conditions can be made on the basis of a careful history and physical and neurological examination; in other words, at an office visit. However, the unexpected happens often enough to justify certain laboratory examinations as a routine. These include Roentgen-rays of the skull, urine and blood examinations, morphological and chemical, and in early cases, or in patients with localized symptoms, spinal fluid examination and possibly a pneumoencephalogram. In our experience, most important of the methods of examination is the recording of the electrical activity of the brain of the patient, and of his parents or other near relatives. These records give some idea of the relative importance of genetic and acquired causes, and of the type, severity, and localization of the disorder.

Corrective treatment is based on the elimination of abnormalities which seem to have a direct responsibility for seizures. The chief of these are tumors or scars of the brain which can be removed by the neurosurgeon, a task requiring the best of skill and judgment.

However, the activity of the brain is indirectly influenced by each body organ and cell and modern physicians do well to repeat some of the rules of health prescribed by Hippocrates. The maintenance of a healthy body and a confident mind, and participation in the work of the world is good medicine for all patients.

If, as happens in at least 95 per cent of patients, neurosurgery has nothing to offer, the physician has to rely chiefly on drug therapy. We preach the necessity of rational therapy, yet for these thousands of years the control of seizures has been empirical. Bromides and phenobarbital apparently act by virtue of their sedative action. They are general soothers of nervous activity and not correctives of the specific disorder of epilepsy. Dilantin sodium, on the other hand, seems to be of specific

value in certain types of epilepsy. Whether it improves the abnormal chemistry of neuronal cells which causes their disorderly and excessive discharge is a subject for future research.

Dilantin sodium was not stumbled on by accident but was the result of planned and patient search. I am sure I express the feelings of tens of thousands when I praise the Chairman of the Fortnight Committee, Dr. Tracy J. Putnam. He, it was who refused to believe that the chance discoveries of Locock and Hauptman could not be improved on by conscientious search. He, with Dr. H. H. Merritt, initiated the studies which led to the demonstration of the superior effectiveness of this non-sedative drug over the previously used sedatives. Dilantin sodium is the drug of choice for most patients subject to seizures. Epilepsy is a tough disease. Dilantin is a sharp weapon which must be wielded skillfully. In the beginning the physician must see the patient at frequent intervals in order to steer him safely between the rocks of toxicity and the whirlpool of continued seizures. The guiding principle is to increase the dose of Dilantin by gradual steps until a maximum therapeutic result is achieved or until symptoms of toxicity appear. The use of Dilantin sodium (phenytoin sodium), as explained in detail by Merritt and Putnam[5] and others[6] need not be repeated here. The matter of dosage requires reiteration. Many physicians who think of phenobarbital and phenytoin sodium in the same quantitative terms, have patients who say, "Dilantin does not seem to work with me." For most patients, the dosage of Dilantin should at least double that of phenobarbital, from 4½ to 9 grains (0.3 to 0.6 gm.) a day.

Pleased as we are with finding this better weapon in our hands, the electroencephalograph warns against undue optimism. Improvement of brain waves usually lags far behind reduction in the number of seizures. Petit mal (dart-and-dome dysrhythmias) are often made worse by Dilantin. The problem of epilepsy will not be solved until cortical dysrhythmia can be controlled.

In addition to drugs, the physician should make use of social and psychological therapy. In my experience, the lot of almost every patient can be improved by attention to these domains. Not only can the physician help his patient by encouragement in intellectual and vocational pursuits, by reorientation of the attitude and hopes of the patient and his family, but he can also do much to correct the present deplorable attitude of the general public. A sign of the times is the formation

of the Laymen's League Against Epilepsy, a national organization with the twin aims of public education and encouragement of research.[7] Local groups are also being organized. Large potentialities for good lie in the New York Society of Convulsive Disorders.

Problems of War and Epilepsy: Our thinking at present revolves around the means for survival in a world convulsed with war. Immediate medical problems are two. First is the duty of keeping epileptics out of the armed forces. The wisdom of this rigid policy may be questioned on the grounds that specially chosen patients when geared to special jobs might be outstandingly useful. In addition, there is the long-standing warning of geneticists that subjecting only the most fit to death and destruction is slow national suicide. Second is the problem of assimilating epileptics into industries which are suddenly labor-hungry. For the person subject to seizures, these two problems are cumulative. A history of seizures automatically throws the draftee into the bottom drawer of the discarded, a drawer marked *4-F*. This procedure, in turn, automatically spoils his chances for work. "If the Army doctors say his physical condition is hopeless," reasons the employer, "I don't want him."

A further barrier to employment which operates in peace, as well as in war times, is the fear of the employer that he may be held responsible for any injury which the epileptic might sustain as a result of a fit "on the job." We have circularized the various states in the Union, asking about compensation codes as they affect the epileptic who may be injured while at work.[8] Replies received from thirty-eight states indicate a lack of any uniformity in the laws or their interpretation. Of court decisions made in five of the states, two ruled that the company was liable even though a seizure caused the fall and the death. "A workman carries with him all his disabilities." At first glance, decisions which provide compensation to the epileptic whatever the circumstances would seem favorable to him. Practically, such decisions are disadvantageous. Because of them, or because of uncertainty in regard to liability, most employers will not knowingly hire an epileptic. It would seem only just that the epileptic should be permitted to waive his rights to compensation when injury results from a spontaneous seizure while at work. In only seven states does there seem to be a provision that an employee may reject the Compensation Act.

Even broader barriers to securing employment are the fear and horror which the sight of a convulsion produces in fellow employees,

the conception of an epileptic as a deteriorated, cantankerous or physically ineffective person who would not be worth his wages, and ignorance of the fact that new methods of diagnosis and treatment are now available. To gather information on the employment record of epileptics we have analyzed the histories of about 1,000 adult clinic and private patients, many of these furnished by colleagues throughout the country. Except for the temporary effects of disuse, the bodily machine of the epileptic is as sound as the average of the population. Not more than 10 or 15 per cent had disturbances of muscular power, coördination, or of control which would prove a serious handicap in physical work. Two-thirds of these patients were judged to be mentally normal by the examining neurologist. Of 608 men who answered the question about their ability to work, 54 per cent were fully able, 24 per cent were partially able, and 22 per cent were unable to work, for the most part because of seizures. Of the 407 women the corresponding percentages were 48 per cent, 34 per cent, and 18 per cent. Of 571 men who answered the question about employment, 97 per cent had formerly been employed, but only 73 per cent had a position when seen by the examining neurologist. Of the 410 males who were employed at the time of examination, 11 per cent were in a profession, 30 per cent in business, 22 per cent in skilled and 37 per cent in unskilled labor. The various occupations were distributed widely over the field of possible occupations.[8]

The adult epileptics in the United States when projected on the number of persons "gainfully employed" form an army of approximately 350,000 persons. A considerable proportion of this force, perhaps a quarter or a third, are unfit for productive activity. Too many of the remaining quarter million persons are denied a share in the work of the world because of public neglect, ignorance and prejudice. Physicians who prescribe inactivity for their patients, who do not know and practice recently acquired facts, who do not join in the campaign against epilepsy, must share the blame.

After the war is over both the relative and the absolute numbers of epileptics will be greatly increased. None will be killed in service but judging from the last war, from 5 to 15 per cent of the brain-wounded will become epileptic. The proportion may be greater now because chemotherapy will save the lives of men with serious brain wounds who before would have died. The hope of decreasing the burden of trau-

matic epilepsy lies with neurosurgery and with the finding of yet more effective anticonvulsant drugs.

Conclusions

In the light of new knowledge gained through use of the electroencephalograph, the term "genetic" is suggested as a substitute for "essential," "idiopathic," or "cryptogenic" epilepsy, and the term "acquired" for "symptomatic" epilepsy. Efforts to prevent epilepsy are more feasible now than formerly. The principal agencies are: (1) the prevention of cerebral dysrhythmia, rather than of epilepsy itself, by means of eugenics; (2) the prevention of acquired conditions which act as a precipitant of seizures, and (3) possibly the treatment of persons who have either hereditary or acquired dysrhythmia in the pre-seizure period.

The important aspects of treatment are removal of acquired causes, the improvement of general physique, the use of anticonvulsant drugs, especially phenytoin sodium, and efforts to strengthen the psychological and social underpinnings of the patient.

War increases both the relative and absolute numbers of epileptics and makes it harder for those rejected by the draft to secure employment. In spite of the needs of industry, now labor-hungry, and in spite of the quarter million epileptics who are physically and mentally able to work, many thousands of persons are refused employment because of popular misinformation and prejudice, and because of compensation laws which may make the employer responsible for injury suffered as a result of a seizure. The efforts of clinicians, investigators and coöperating laymen should be intensified in and after this war period.

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SOME MEDICAL PROBLEMS OF VESICANT CHEMICAL WARFARE AGENTS AS AFFECTING CIVILIAN POPULATIONS*

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CHEMICAL warfare agents are simply military weapons, highly efficient under certain circumstances. Whenever it is necessary to use them against civilian populations, these will be used, especially when the danger of retaliation is not feared. There should be no overemphasis of the danger of chemical warfare against civilians neither should there be a complete denial of the possibilities of their use. If chemical warfare agents, especially the vesicants, are employed against civilians, they will be projected from airplanes in the form of sprays or bombs, or they will be used in varied sabotage techniques. Because of a fear complex of this phase of warfare, without actually using such compounds, the enemy can accomplish a great deal by merely suggesting that they might be used. European and Japanese peoples have had long training programs in chemical warfare defense.

Because of many obvious factors, chemical warfare defense training as regards civilians in this country is still in its early infancy. Fortunately, our army possesses excellent gas discipline and the Chemical Warfare Service is keenly alive to its present responsibilities in all phases of chemical warfare. At present, chemical warfare has not been used against civilians so that all civilian training must be done by theoretical principles. It should be added that for the civilian populace less disciplined and less well organized than the army, training for defense against chemicals is exceedingly difficult. Civilian physicians are very important parts of this defense scheme. They must first learn and receive training themselves before becoming part of the program. New York State was

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the first to develop, for the physician, a definite teaching program in the medical aspects of chemical warfare.[1]

The highly effective chemical warfare agents, known as vesicants, or blistering agents are responsible for most of the difficult problems of civilian defense. Mustard agent, a term preferred to "mustard gas," BB′ dichloro-diethyl sulfide ($Cl\ CH_2\ CH_2)_2\ S$, has been known since 1854 and had been used extensively in the World War I and in the Italo-Ethiopian War.

Mustard was introduced in World War I to cause casualties even if the soldier was protected by a good gas mask. This agent is a clear oily substance when pure, brownish or blackish in color when used in the field. The odor is interpreted variously as that of garlic, mustard, or horseradish. The stains on the ground resemble those of a thin machine oil. Because of its low vapor pressure (0.11 mm at 20° C) mustard is remarkably persistent, remains where it is discharged for considerable periods of time especially in areas where ventilation is poor. Sparingly soluble in water, this material is soluble in fats, oils and also in the organic solvents. It is also soluble to some degree in rubber. Oilskins, cellophane materials, and the like resist penetration of mustard. To reduce the melting point, carbon tetrachloride (15 per cent) is used. Phosgene, the pulmonary irritant, may also be used as solvent. Mustard agent is an efficient material by virtue of its toxicity, persistency, and penetrability.

But with all this long history of actual use and in spite of some published reports to the contrary,[2,3] little is known of the mechanism of its local action. There is no immediate sensation on cutaneous contact, even with heavy splashes. The agent penetrates the cutaneous barrier both through the epidermis and into glandular orifices of the skin surface. The degree and rate of penetration depend, of course, on such factors as the concentration maintained on the surface, the local character of the skin as regards kerato-hyalin mass and thickness of the epidermis, the number of gland appendages, etc. The solvent may aid cutaneous penetration. To demonstrate the toxicity of this chemical warfare agent, 0.005 milligrams per liter of air is the figure for vesicant concentration. Most of the agent which does not vaporize from the surface of the skin or which is not removed mechanically by absorbents, solvents, or detergents or which is not changed chemically, passes into the epidermis and derma. There it reacts locally after "intracellular ab-

sorption," and produces cellular destruction of varying intensity depending upon the concentration of the agent and somewhat on the sensitivity of the individual to the agent. The latent period varies usually from six to eight hours. Then, erythema, edema, vesiculation and perhaps necrosis, develop in order. Mustard is a strong eczematogenic agent and individuals who work with it for any length of time become sensitized easily. Various forms of maculo-papular, urticarial and vesicular reactions can then be produced by much weaker concentrations of the agent, and even by inhalation. There may be also focal reactions in sites of old, healed mustard lesions. These focal reactions in sites of old burns have been observed following inhalation of very weak concentrations of mustard agent with the skin covered completely. In sensitized individuals pompholyx-like eruptions have also been observed following inhalation or cutaneous contact distant from the hands. Hypersensitivity of viscera other than the skin has not been reported as yet. The negro is certainly less sensitive to vesicants just as he is certainly less sensitive to the poison ivy oleoresin. The published reports of E. K. Marshall, Jr. and his co-workers and various Italian investigators on work with the natives of Africa bear out this observation. In our work with a group of twelve negro patients, no vesicles could be produced with concentrations giving severe vesiculo-bullous reactions on a control group of white individuals. A vesicle was produced however on a dark skinned negro who had a contact dermatitis at the time the test was done. An attempt was made to sensitize three negroes by daily applications of mustard agent for three weeks. This was unsuccessful. No reasons are known definitely for this difference in sensitivity. This decreased sensitivity of the negro to the vesicants should be considered in the civilian defense plans. We have had negative results with passive-transfer tests in regard to mustard sensitivity. Some mustard may be carried unchanged to distant viscera and there produce the phenomenon of cellular destruction. More frequently, however, changes in distant viscera may occur following the local primary reaction of the vesicant or some complicating local factor such as infection. In a similar fashion any unprotected surface of the body will react to the vesicant. Such surfaces include the cornea and conjunctiva of the eye, the entire respiratory tract[4] or, following ingestion, the gastroenteric tract.[4] Such is a very general and brief outline of the picture of vesicant action. This is not an explanation of the mechanism of the action. It should be added that

these problems in regard to the mechanism of vesication have exposed our ignorance of many of the basic mechanisms of physiology of the skin chiefly as regards absorption and adsorption by the skin and also the mechanism of skin sensitizations, and even of rational cutaneous therapy based on physiologic and chemical principles.

The vesicle may continue to enlarge for several days. This change is important to remember in regard to local therapy. These changes are associated with severe pruritus which persists for some time and which provokes, through scratching, secondary eczematization and infection. Healing is prolonged unusually for an ordinary vesicular contact dermatitis. Here is one point where the analogy to poison ivy dermatitis does not hold. To some extent, this slow healing is due to the depth of the lesion produced, much deeper than the usual blister of a poison ivy dermatitis. Vascular damage is reported to be another cause of this apparently slow healing process. Secondary infection may ensue. There is some disagreement as to the frequency of secondary infection. We have seen only one instance of secondary infection from the cutaneous testing to mustard agent of a large number of physicians. Of course, under field conditions, chances for secondary infection of cutaneous lesions are more numerous. The patient with an extensive mustard agent dermatitis does not present the systemic picture of a thermal burn of the same degree, but rather the mild toxic state of a severe poison ivy dermatitis. However, more studies are needed on the systemic reactions from pure cutaneous contact.

Of more clinical importance is the irritation of the respiratory tract, first manifested by sneezing, hoarseness, aphonia and then by signs of pulmonary irritation, of the so-called first lines of pulmonary defense, the trachea and larger bronchi. Then, follows a secondary pneumonia of a mixed infection type. This pneumonia is chiefly responsible for the death of the individual "gassed" by mustard. In the last war the slight eye injury, with little or no corneal involvement, was the most frequent type found. At present, when airplane projection will be used, more cases of moderate to severe corneal and conjunctival damage will be found. Gastroenteric reactions will be more apt to occur from the ingestion of contaminated food or even of water where mustard, only slowly hydrolized by the water, will still be irritant. These gastroenteric reactions were noted especially in the animals of the Ethiopians in the Italo-Ethiopian war. Sequelae following mustardization will occur from

any viscera damaged but the frequency of complication, even of permanent eye and pulmonary damage, at least in World War I, was surprisingly small.[5] Whether the incidence of such sequelae will continue to be low with civilians who have less gas discipline, less efficient protection and less strong physical and psychological make-ups than soldiers remains to be seen. Scarring pigmentation, and artefactal lesions, because of the pruritus, may follow the dermatitis.

Now, an individual protected by a gas mask and exposed to mustard agent, liquid or vapor, is not an immediate casualty. He is able to carry on his duties for some hours. Even then when lesions appear, he is uncomfortable but still able to do some work. Moreover, after a prolonged period of hospitalization he may return to active duty. In an effort to "correct" some of these deficiencies, another agent was developed by the Army at the end of the war. This was B chlorovinyldichlorarsine, lewisite, Cl CH: CH As Cl_2, an arsenical compound. This material was first initiated at the American University and then elaborated on by Professor Lee Lewis of the Army Chemical Warfare Service. This compound was supposed to include many of the properties of the other agents used in chemical warfare. The appearance of the pure and "field" mixtures of lewisite is similar to that of mustard, but the vapor pressure of lewisite is only 0.4 mm at 20° C. This makes it less persistent than mustard. Its freezing point 5° C. (app.) is lower however than that of mustard, 14.4° C., so that lewisite mixtures are more apt to be used in colder climates. The odor of pure lewisite is pungent and irritant. Burning of the eyes and nose and tightness of the chest are symptoms produced by smelling pure lewisite. The odor of the product used in the field and the odor of material remaining on laboratory equipment is similar to that of geraniums. This odor may be due to decomposition products of lewisite. There is an immediate burning and pricking of the skin after lewisite contact, even from the vapor. The development of the vesicle is more rapid, twenty to thirty minutes, and the vesicle is much larger than the mustard vesicle and in its complete development presents no areola. However, this red areola does become marked during the latter stages of the development of the lesion. Although the cloudy fluid of the lewisite blister is supposed to contain arsenic, we have not been able to detect arsenic, with sensitive methods, by analyzing the contents of the twenty-four hour and older blister. In one instance, the cutaneous cap of the blister was included in the analysis. We have not

examined blisters less than twenty-four hours old. It has been our experience also that this blister fluid of the older blister, is not irritating to the adjacent skin nor to the skin of other individuals. This material was applied to other individuals by the patch test technique. Stains for arsenic crystals with the sulphide and bismuth-sulphide techniques reveal, in man, crystals of arsenic salts scattered deeply in the derma and beyond the confines of the visible inflammatory process. Keller[6] in his series of one hundred patients, found no secondary infection of the lewisite vesicle in spite of its purulent contents. We have cultured the contents of the four and five day old lewisite blister in ten patients. In one patient gram positive cocci were found on direct smear and also on culture. The patient had a concomitant staphylococcal ecthyma. In another patient gram positive cocci were found only on culture, not on direct smear. It was assumed that this culture was from contamination.

Keller worked with mustard and lewisite in benzol and tested white individuals, by the drop method, on the exposed skin of the back. He reported that in spite of the higher concentrations of lewisite which he used, this agent caused weaker reactions on the skin than the mustard. He did admit, however, that the threshold dose varies widely with individual sensitivity. Arsenical poisoning results from lewisite contact and the intensity of systemic poisoning varies with the amount of arsenic absorbed by the tissues. Pulmonary edema in animals may be produced by cutaneous contact. Bile duct necrosis, without liver drainage, has also been mentioned in animals following application of the lewisite to the skin.[7] As with mustard, similar and perhaps more severe irritations of the eye and respiratory tract may follow contact with lewisite. Another arsenical vesicant agent more important in the military situation than in the civilian area is the less persistent ethyldichlorarsine, C_2H_5 As Cl_2. In some of the casualties from this agent in World War I paronychiae were reported. This is less effective than lewisite. Many other compounds have been examined and continue to be examined for vesicant action. For the civilian, however, mustard and lewisite should be his chief concerns.

A very important use of these agents in regard to civilian populations is their role in sabotage. It is scarcely practical to contaminate large water supplies by mustard or lewisite. But small unprotected water supplies can be poisoned. Undissolved mustard may remain for several

weeks at the bottom, the soluble portion slowly hydrolized.

$$(Cl\ CH_2\ CH_2)_2\ S + 2HOH \rightarrow 2HCl + (CH_2\ OH\ CH_2)_2S$$

$(CH_2\ OH\ CH_2)_2S$ is thiodiglycol and is non-toxic. The Army considers contamination of water more than 500 p.p.m. of mustard as unfit for drinking purposes. Boiling will render water safe. With the arsenical agents, soluble arsenious oxides can not be removed by ordinary water purification processes. Lewisite is hydrolized rapidly by water, and the chlorovinylarsenious oxide formed is relatively unsoluble but is still a vesicant, less active however, than lewisite.

$$Cl\ CH{:}CH\ As\ Cl_2 + HOH \rightarrow Cl\ CH{:}\ CH\ As\ O + 2HCl$$

"If the arsenic content does not exceed one to five p.p.m. the water would be safe to use for periods varying from one day for higher concentrations, to one week for lower concentration. If larger quantities of arsenic are found, or if other non-contaminated supplies are available, the water should be pumped to waste."[8]

The vesicant agents also lend themselves for sabotage purposes in the industrial plant. Since mustard and lewisite are both soluble in oils, contamination of all machine oils by these agents is possible and then the machine itself can become dangerous for the workmen to touch and perhaps, difficult to decontaminate. Machine tools may be contaminated deliberately with vesicants so that the unsuspecting workman may get severe irritations of the skin from contact with these tools. Warehouses, especially food depots, may be sabotaged by mustard and lewisite. Expert advice will have to be secured in order to determine the extent of contamination and proper technique of decontamination of the foods. Shipping areas may be sabotaged by mustard and lewisite, by means of land mines, and these areas will be dangerous until decontaminated. Sometimes, the only thing necessary to produce panic is to suggest that chemical warfare agents may have been used or to use harmless materials with odors of mustard or lewisite and valuable working time will be lost until detection services and trained technical gas officers disprove the rumor.

It is possible, of course, to diagnose contamination of an individual before clinical signs ensue. This may be done by the history of exposure which includes degree of protection and the extent of personal decontamination, the appearance of stains on clothing and skin, the odor of the casualty, and the use of detector papers which change color on contact with the agents. Most of these detector papers at present require

fairly high concentrations of agent to affect a color change. For practical purposes, however, it is sufficient to diagnose simply vesicant contamination since the details of prophylaxis are really not specific enough under field conditions, nor do they warrant time lost in attempting a differential diagnosis.

The Medical Division of the Office of Civilian Defense has given adequate instructions[9,10,11,12,13,14] in regard to protecting individuals from chemical warfare agents. It is important to know and to teach these official recommendations since decontamination of a potential casualty can be done most promptly and therefore most effectively by the individual himself. To do this he must be trained correctly. The individual, at present should not be taught to rely on chance evacuation to an established medical unit nor to make too many demands on official personnel, such as Air Raid Wardens, during and shortly after raids. For those civilians required to be outside during a chemical warfare attack, adequate protection from vesicants will be obtained. A basic knowledge of these agents will aid individuals in the improvisation of equipment for surprise attacks or for unprotected groups. Many types of improvised masks have been suggested but not too much reliance should be placed in these, unless they have been made with great care and have been approved by the Office of Civilian Defense or by the Army Chemical Warfare Service. A false sense of security may be given and since many of these agents have insidious actions, the inefficiencies will not be detected until it is too late. The heavy handkerchief soaked in baking soda solution or sodium hypochlorite solution is just as effective for brief periods. With vesicants, the eyes must be protected by attempting to keep them closed if possible and not rubbing them, or by some sort of close fitting cellophane or plastic goggles or industrial goggle or even underwater goggles. Bathing caps, hats and umbrellas will protect head and scalp especially from aircraft spray. This is important because adequate decontamination of hair is difficult. To protect the body, any type of impermeable material may be used. These include, of course, such materials as raincoats, cellophane (heavy laminated types), aprons and sleevlets, oil cloths, shower curtains, etc. Heavy rubber gloves will protect the hands and heavy rubber boots or galoshes will protect the feet. We have had the opportunity to observe an individual who suffered vesicular lesions on the foot from mustard which penetrated through the shoe. After an accident in the laboratory the shoes

and clothes were inspected carefully and pronounced free of contamination. The individual was examined some hours later again. Yet, some fourteen hours after the accident, a diffuse erythema appeared over the dorsum of the toes of the right foot. This was associated with severe pruritus. Later, two small vesicular lesions developed. The shoe was discarded.

The official gas masks and complete anti-gas clothing either of the oil-skin type or of the impregnated type, cotton clothing impregnated with special solutions of the Army Chemical Warfare Service, constitute the official protective measures for the individual. Many medical problems arise in regards to these individual protective measures against vesicants. For the healthy individual the wearing of a gas mask produces no significant changes in his cardiovascular and respiratory dynamics. There are the questions of special masks for infants and children, for invalids with chronic cardiovascular and pulmonary conditions, of special masks for head injury cases, etc. Of course, the obvious answer to these questions would be evacuation in advance of such individuals. Moreover, if clothing is impervious to the passage of the vesicants, likewise it is impervious to the passage of air. In such outfits, heat loss of body is seriously interfered with since there is little opportunity for heat loss by physical factors such as the evaporation of sweat and radiation. When one attempts to do some degree of exercise in these suits the limits of tolerance are reached very quickly. Splashing the suit with cold water has been tried to lower the temperature of the outfit. In hot weather the usual limit is about thirty minutes before heat stroke may ensue. Strong individuals should be chosen for those units, such as decontamination squads, required to work in such suits. Cotton suits impregnated may be worn for longer periods of time but these suits do not protect against heavy splashes of liquid vesicants on their surface.

Because of the rapid absorption of the vesicants by the skin and by the eye, ideal prophylactic therapy must be done as rapidly as possible. For liquid splashes on the skin and for eye contamination, prophylaxis must be done at once. After about five minutes of liquid contamination of the skin, prophylaxis is not effective.[9] If one waits until a medical installation is reached it may be too late to prevent any lesions. Therefore, it is important that the concept of personal decontamination be emphasized for individuals with partial or complete lack of protection against vesicants. The mechanisms of surface decontamination include

absorption, adsorption, hydrolysis and oxidation. The details of these processes are given in official publications of the Medical Division of the Office of Civilian Defense. There is some confusion in regard to recommendations as to the uses of solvents. With careful technique, gentle blotting from the periphery of the contaminated spot to the center, the organic solvents in which mustard or lewisite are soluble, may remove an appreciable amount of unabsorbed agent from the skin surfaces and from the gland orifices. If solvent is used too carelessly or rubbed too vigorously, it may actually favor absorption of agent into the skin. Work continues to be done on the forms of oxidizing agents to destroy or to render less soluble or less toxic any vesicant agent remaining on the skin. It is extremely doubtful whether these oxidizing agents can affect agents absorbed into the skin. The oldest and most active oxidizing agent forementioned is bleaching powder which reacts with mustard to form dichloroethyl sulfoxide.

$$(Cl\ CH_2\ CH_2)_2S + Ca\ O\ Cl_2 \rightarrow (Cl\ CH_2\ CH_2)_2\ S{=}O + Ca\ Cl_2$$

With some oxidizing agents, under certain conditions, the sulfone may be formed. The bleaching powder will oxidize lewisite also. Relatively little bleaching powder will be available for civilian use at present. Possibly its best substitute at present for the use on streets, buildings, apparatus, etc. is the dual injector decontamination unit apparatus of lime slurry and chlorine gas.[10] The chlorine content of this mixture is low however. Because of its highly irritant properties bleach has little use in skin decontamination save where it can be removed quickly.[15] When no other materials are available, bleach mixture may be used for general sponging of the body; this mixture should contain four grams of bleach powder to five hundred millitres of water. In the civilian protection scheme, household buffered sodium hypochlorite mixtures, containing about 5 per cent of sodium hypochlorite will be available for decontamination of the hair and skin.[16] The Protective Cream of the Army Chemical Warfare Service is excellent protection against mustard and even against lewisite. For lewisite this Protective Cream offers protection only when the cream is on the skin before lewisite contact. With regard to lewisite the peroxides are preferred at present as the decontamination agents.

$$Cl\ CH{:}\ CH\ As\ Cl_2 + O + {}_2HOH \rightarrow Cl\ CH{:}\ CH\ As{=}O + {}_2H\ Cl$$

These peroxides must be used within five minutes after contact with the agent. Hydrogen peroxide, zinc peroxide, benzoyl peroxide, urea peroxide, and sodium perborate, are some of the compounds used. If these compounds are used one must regard critically their oxygen activity and their stability. Unlike with mustard, water is possibly the best practical prophylactic agent for lewisite since the hydrolysis is so rapid. The skin surface must be rinsed well afterwards. Splashes of vesicant on the skin are definite medical emergencies and fraction of minutes count. It is important to emphasize that eye contamination is also a definite medical emergency. In the eye, no oxidizing agents or strong solvents should be used since any corneal damage which these materials cause will make for deeper lesions by the vesicants. Correct gentle irrigations with saline or 2 per cent sodium bicarbonate solutions are recommended. There is some controversy at present as to whether irrigation should be continued when the eye lesions begin to develop. There are no good materials for instillations in the eye for prophylaxis before contact. Here, only the improvised or officially recommended mechanical devices for protection will be effective. Since tiny droplets from airplane spray are very dangerous to the eyes, individuals such as airplane spotters and the like should be protected in advance.

When the vesicant lesion develops there is no longer any question of so-called specific therapy. The materials recommended for prophylaxis can not be used here since these chemicals are too irritant for damaged tissues. There is need at present for substances which can function both as effective prophylactic agents and non-irritant therapeutic materials. With the development of the vesicle and bulla the local treatment[17,18] is similar to that of a severe poison ivy dermatitis. It is only some hours, possibly not until the next day, after the chemical warfare attack that these lesions will appear and the casualty will become uncomfortable and then the rush to the casualty stations and hospitals begins. All efforts should be made to keep these lesions as clean as possible.[19] Debridement should be done. For the small lesion under 0.5-1.0 cm. healing will occur no matter what form of local therapy is used. These treatments may include solutions of isoamyl salicylate, the conventional wet compresses of diluted alum subacetate, permanganate, etc. or the sulfadiazine suspensions, either in water emulsions types or in collodion, or with the crusting techniques of tannic acid-silver nitrate combinations. As for the larger lesions, it is well not to apply crusting

techniques too early since, unlike the bullae from thermal burns, the bullae from mustard and lewisite may continue to advance for forty-eight hours and the edge of the formed crust may not extend up to the edge of normal skin. Cold compresses help to relieve some of the severe pruritus ever present. Later, various anti-pruritic mixtures may be used. If nursing services are restricted, crusting techniques should be preferred. As with thermal burns, crusting techniques should not be used on the face, genitalia, hands and feet. It should be emphasized that the purposes of local therapy are to make the patient more comfortable, to prevent secondary eczematization and infection from scratching. Because of the systemic poisoning from lewisite contact, efforts should be made to remove or immobilize arsenic in the tissue adjacent to the contact site so that there will not be continued absorption from this area. Of course, the ideal method to accomplish that is by complete excision, but this is scarcely practical. Efforts to keep serum oozing from the lewisite area, injections of oxidizing agents (type?) into the contaminated tissues, peroxides locally on the area, ferric hydroxide pastes, have all been suggested as local therapeutic materials. The question of sulfa therapy for prophylaxis in extensive mustard or lewisite lesions has not been determined as yet. We have demonstrated sulfathiazole in the bullae of dermatitis herpetiformis. We have also demonstrated sulfa-compounds in the experimental mustard areas of animals.

Save for signs of arsenical poisonings with the arsenical vesicants and signs of pulmonary irritations in an unprotected individual, it is unusual to find any marked systemic reactions early in the course of even severe vesicant casualties. There is not much data available at present on protein balance or hemoconcentration in extensive vesicant cases. However, if plasma is indicated it should be given. When there are obvious signs of pulmonary irritation, cough, etc., in addition to the usual measures, sulfadiazine may be given as prophylaxis against the secondary bronchopneumonia which is almost certain to develop. For the arsenical poisoning such measures as repeated biliary draining, glucose, vitamins, etc. may be used. The treatment of eye injuries should be left to the ophthalmologist.

Those who preach the horror of chemical warfare forget the casualty figures of the past war.[20] In the American Army, of 70,752 casualties from gas only 1421 or 2 per cent died. Of these 70,752 gas casualties there were 27,711 casualties from mustard with 599 deaths or mor-

tality of a little over 2 per cent. With none of the horrible scars or deformities and with considerably lower incidence of blindness, chemical warfare is definitely easier on the casualty. There are no figures available as to the total mustard casualties of the Italo-Ethiopian War nor are there any figures available as to the casualties from the uses of lewisite mixtures by the Japanese against the Chinese.

Because of the long convalescence and the discomfort of the patient, all extensive cases should be hospital cases. The patients should be kept on bright, cheerful wards preferably under the care of dermatologists since these physicians are accustomed to treat such pruritic resistant dermatoses as result from mustard or lewisite. Complications such as one would suspect in similar types of cases may develop. For civilian groups individuals will be found to focus attention on their eyes, skin, respiratory tract or even cardiovascular system and to express psychoneurotic symptoms in these areas. Because of the undue fear of chemical warfare and because of overemphasis of complications, such psychoneurotic reactions should be expected to come frequently, if mass raids are made. The prevention of such reactions should be emphasized through all phases of the civilian protection scheme by repeated complete examinations, reassurance of absence of all findings, separation of such cases from convalescent vesicant cases. When the patient is discharged, it should be emphasized that no additional medical supervision is needed. Otherwise, compensation burdens for the community will be acquired for years to come.

The physician must realize that complex situations are suggested when methods of defense of civilian populations against chemical warfare are considered. The problem is more difficult when one realizes that all questions in regard to chemical warfare against civilians are on a purely theoretical basis at present. The difficulties of protection against the vesicants arise chiefly from the facts that these agents are toxic in minute quantities, can persist for long periods of time after discharge and that they can penetrate ordinary clothing and many building materials so effectively. First, the physician must educate himself.[21] He is helped in this by the state educational programs in medical aspects of chemical warfare such as the state of New York has developed in each of its medical schools. Since the field of chemical warfare is of necessity a military one, newer developments will be made available only when possible. As much as he may detest and like to disregard them,

the physician must learn some details of organization because otherwise his theoretical plans of prophylaxis and therapy will not be able to be carried out. The physician will need considerable technical help,[22,23] because the field of vesicant agents has so many technical problems referrable to the detection of agents, the contamination of streets, buildings, food and water supplies, and the construction of special medical stations, with casualty stations and with hospitals, where chemical warfare cases can be handled with safety to the attending personnel and with justice to the patient himself. This technical help will be engineers, chemists, etc. who will be trained as non-medical gas officers. To prevent chemical warfare sabotage in large plants special plant gas officers will be trained. The evacuation of chemical warfare casualties from the first episode after emergency care for the casualty by the air raid warden, to the hospitalization of the severe case with complicating eye injury, pulmonary irritation, associated hemorrhage or shock, is an extremely complicated scheme. Each unit will have to work out its own evacuation procedures. Plans can be made and even extensive training problems can be adapted in the absence of equipment. Casualty figures in an area prepared and trained in advance will be low.

When the physician understands and learns the uses and limitations of chemical warfare, the principles of prevention and treatment, he will not be panic stricken upon the introduction of any new agents. If odors are absent or disguised, if combinations of agents are used, if other vesicants with other systemic effects are employed, the trained physician can still use the same principles which he has learned with mustard and lewisite as his training problem examples. Chemical warfare advances are definitely military secrets and in this total war the physician must learn to accept this. With his background in chemical warfare training he will adapt any new details easily and effectively when these details are furnished.

Conclusions

The vesicant agents, chiefly mustard and lewisite, because of their toxicity, persistency and penetrability are responsible for most of the complexities of the scheme for the defense of civilian populations against chemical warfare. The physician is a very important part of this defense scheme. He must secure special training in the medical aspects of chemical warfare to carry out his role. Such training programs are available

at present. Little is known of the theories of the action of vesicants. A great deal is known of their toxicology and pathology and of their specific prophylaxis. The treatment of the resulting lesion is purely symptomatic, namely that of a vesiculo-bullous, resistant and pruritic dermatosis with strong sensitizing properties. Mustard and lewisite dermatitis are not strange or mysterious maladies to the dermatologist. For those vesicants with systemic poisoning components, such as the arsenical compound, lewisite, therapy for this systemic phase should be given also. Decontamination of an individual will be done most effectively by the individual himself. The evacuation of the actual casualty must be done in a different mode from other warfare casualties since all cases contaminated by vesicants are dangerous to handle. In the technical phases of decontamination the physician will have the help of a trained non-medical gas officer and the industrial physician will have the help of his plant gas officer. The educational program of the physician must also include measures to prevent psychoneuroses which would be expected in large civilian groups. With his knowledge of the principles of prevention and therapy, the trained physician will be able to cope with any new agents which may be used. In all these ways, the physician will learn the real role of chemical warfare against civilians and will avoid acquiring for himself and consequently spreading by teaching, those factors of overemphasis, exaggerations, panic and fears, all reactions so earnestly desired by enemy propaganda services.

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*INTERNATIONAL SOCIETY OF SURGERY REORGANIZED HEADQUARTERS TRANSFERRED FROM BELGIUM TO THE UNITED STATES**

By a vote of the delegates from all of the affiliated societies of the Americas, representing Argentina, Brazil, Canada, Cuba, Ecuador, Guatemala, Mexico, Paraguay, Peru, United States, Uruguay and Venezuela, the headquarters of the International Society of Surgery was provisionally transferred from its European headquarters in Brussels, Belgium, to the United States. More specifically, the headquarters has been established in the Inter America Division of The New York Academy of Medicine in New York City.

In explaining the need for the change in headquarters, Dr. Rudolph Matas of New Orleans, Acting Secretary and Treasurer of the International Society of Surgery said:

"The German occupation of Belgium and the Nazi devastation of the rest of Europe and all the other war-torn nations, had virtually restricted the international relations of the Society to the Western Hemisphere where its fellowship is widely spread through its affiliated branches in North, Central and South America.

"The Executive Committee of the United States Division, the largest, most active contributor to its transaction, felt it their duty conjointly with their Latin American colleagues to rescue the Society out of the perils of the European conflagration. The first steps were taken November 1941 at Boston but no final action could be taken to transfer the official sanctum in Brussels to America without the concurrence and approval of all the affiliated branches in America."

The act by which the transference of the International Society of Surgery from Europe to the United States was effected, was signed either personally or by proxy by the Delegates from all the affiliated societies of the Americas.

By the action of the Council of Delegates, the official seat of the Society will be established in the Inter-America Division of the New York Academy of Medicine, directed by Dr. Mahlon Ashford, where Dr. Enrique J. Cervantes, Assistant Secretary-Treasurer of the Executive Committee, Editor of "América Clínica," the official organ of the society and Editor and Secretary of the Hispanic-American Medical Society, will be able to render service to the Fellows of the Society and medical visitors hailing from the Latin American countries.

The affairs of the International Society of Surgery are to be administered by an Executive Committee composed of the following: Dr. Elliott C. Cutler, Col. M. C., U. S. Army, Chairman in Absentia, Dr. Eugene Pool, Dr. Arthur W. Allen and Dr. Rudolph Matas, Acting Secretary and Treasurer.

The meeting was presided over by Dr. Eugene Pool, who serves as Acting Chairman of the Executive Committee for the United States, in the absence of Colonel Elliott C. Cutler, now at the front.

Dr. José Arce, Dean of the University of Buenos Aires, will serve as Acting President of the International Society of Surgery in the absence of Professor L. Meyer of Brussels, detained in Belgium by Nazi compulsion.

The revision of the Constitution adopted on Thursday, November 12, 1942 was prepared by Dr. Rudolph Matas of New Orleans, former President of the Society and now Acting Secretary-Treasurer. A representative group of Fellows from New York and elsewhere signed the Act of reorganization, as witnesses of the signing of the Act by the delegates of the Governing Council, among whom were Drs. Walter Estell Lee of Philadelphia, Russell S. Fowler, Ralph Colp, Edwin G. Ramsdell, Frederick W. Bancroft, Howard Lillienthal, Charles Elsberg, Seward Erdman, Carl Eggers, Henry Lyle and others elsewhere, by proxy.

The establishment of an Inter-America Division of the New York Academy, with the opening of the editorial offices of "América Clínica," the most widely read of Spanish-Portuguese medical publications in South, Central America and Mexico and the opening of an Inter America Bureau to render a free service for medical information, has proved probably the most valuable of all the practical contributions that the United States has made to the cause of Latin American good will and friendship.

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* Contributed by Dr. Rudolph Matas, November 28, 1942.